AD_____
(Leave blank)

Award Number: W81XWH-09-2-0184

TITLE: Near-infrared spectroscopy to reduce prophylactic fasciotomies for and missed cases of acute compartment syndrome in soldiers injured in OEF/OIF

PRINCIPAL INVESTIGATOR: LTC Brett Freedman, MD

CONTRACTING ORGANIZATION: The Geneva Foundation

Tacoma, WA 98402

REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:
☒ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
1 Oct 2013	ANNUAL REPORT	30 Sep 2012 - 29 Sept 2013

4. TITLE AND SUBTITLE
Near Infra-Red Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-2-0184

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Freedman, Brett – Principal Investigator

email: brett.freedman@amedd.army.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Geneva Foundation

Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The research project is a three-part project to validate the accuracy and reliability of a specific NIRS sensor (Equanox, Nonin, Inc, Plymouth, MN) in diagnosing acute compartment syndrome in injured combat soldiers. Part 1 is a series of two observational studies, the first of which was completed at Landstuhl Regional Medical Center during year 1. The second clinical study was originally planned to be conducted in theatre in Afghanistan and Iraq, but had to be transitioned to a FDA-regulated study conducted under an abbreviated IDE within the USA. This study was established in Period 3 and completed in Period 4. Part 2 of the project involves animal studies to address issues raised in clinical testing and furthering understanding of NIRS response to ACS. The first animal study was completed in Year 2 of this award, and a second study using a different ACS model was completed in the current reporting period. Part 3 of this project is the translation of the current technology into a validated, FDA approved format. Data collected in Parts 1 and 2 will be used as the basis for developing a NIRS-based diagnostic algorithm that will be validated in a subsequent clinical trial.

15. SUBJECT TERMS
Near Infra-Red Spectroscopy, acute compartment syndrome

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	57	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

INTRODUCTION

This research covered under this award was a three-part project planned to be conducted over three years to validate the accuracy and reliability of using Near Infrared Spectroscopy (NIRS) to diagnose acute compartment syndrome (ACS) in combat soldiers and civilians suffering high energy trauma to the lower extremities. Part 1 was two clinical observational studies. The first part (Phase I) was conducted at Landstuhl Regional Medical Center and was started in the first year of this award and completed on time and on budget. The second study (Phase 2) was originally planned to be conducted in theater at Level III CSHs in Afghanistan and Iraq with support from the Joint Combat Casualty Research Team (JC2RT) and a researcher specifically deployed to lead this study in-theater. However, during the protocol review process, USAMRMC petitioned for a pre-IDE determination from the FDA, and it was decided that the study needed to be conducted as an FDA-regulated study (with "abbreviated requirements"), and was transitioned to three civilian hospitals in the state of Georgia. This transition caused over 12 months delay in initiating the study, as described in our previous annual report. Because of this delay, we were granted an extension for this award into a fourth year. Now, as we approach the conclusion of the fourth year of funding, we report that the Phase 2 study has also been completed, marking successful completion of the original tasks outlined in this grants' Statement of Work.

Part 2 (Task 3) of this award used porcine models of ACS to further evaluate and validate the clinical utility of using continuous NIRS monitoring to diagnose ACS. The initial experiments using albumin infusion and contusion/albumin infusions models for inducing ACS were successfully completed on target by the end of the second year of this grant. These studies demonstrated that NIRS measurement of hemoglobin oxygen saturation in the tibial compartment provided reliable and sensitive correlation to increases and decreases in intra-compartment pressure and intra-compartment perfusion pressure. In year 3, we built on the success of the animal experiments by employing a second model of tibial compartment syndrome, which uses an inflatable balloon to increase intra-compartment pressure. This model was originally conceived in the US Army Institute of Surgical Research. This demonstrated that NIRS accurately detected a critical hypoperfusion that occurs in the setting of ACS. In the controlled state of an animal model, our series of studies has built on prior knowledge to provide compelling evidence that NIRS can serve as an accurate and reliable noninvasive means for diagnosing ACS. In the final year, we have (under a no-cost extension for the UGA sub-award) designed and will complete animal testing to evaluate the NIRS data obtained when ACS is "missed" or delayed in diagnosis, which is known to be a clinically devastating occurrence. In short, our animal testing and that in existence makes us confident that NIRS can accurately monitor the physiological states associated with severe leg injury and ACS, in the controlled setting of an animal model. The challenges encountered in the clinical setting are discussed below.

The final part of this project (Tasks 4 – 6) included the translation of the current technology into a proven means for detecting the presence of critical hypoperfusion of the leg compartments indicative of acute compartment syndrome. The data collected in our Phase 1 and 2 clinical studies and the animal studies will be used to optimize the technology, develop a diagnostic algorithm and ultimately form the basis for a subsequent clinical trial to validate this algorithm and lead to the first FDA indicated diagnostic device for ACS. The current FDA approved indication for the NIRS device used in our clinical studies (the Nonin Equanox^{TM} 7600 oximeter) is for monitoring regional tissue oxygenation. This device has been validated and is currently marketed as a means for detecting altered states of perfusion in normal (i.e. not traumatically injured, specifically cerebral) tissue. Our research and development initiative has pushed this technology to its limits, by seeking to monitor altered perfusion states in abnormal (i.e. traumatically injured) somatic tissue. In Period 4, our industry partner and this research team have sought to identify areas to improve this technology in the reduction to practice of an ACS diagnostic device. The FDA indication we will seek to develop,

submit and defend using the results of the clinical and animal studies conducted under this grant and the study to follow is a diagnostic indication such that the device can be approved to provide information that directly impacts clinical decision-making. This function will meet the critical unmet need in combat casualty care originally identified in our grant proposal.

BODY

The primary goal of work conducted in Period 4 was to complete the Phase 2 clinical study that was initiated in Period 3. At the conclusion of the previous period, the study had been initiated at all three sites, and each site had enrolled subjects. At the conclusion of the current period enrollment into the study has been completed and we are preparing to close out the study.

TASK 1: Human Use Study – Phase 1

1a – g: All tasks completed on time and within budget in Periods 1 and 2

TASK 2: Human Use Study – Phase 2

2a – c: Tasks completed in Period 2

2d: Conduct Phase 2 Prospective Observational Study

The Phase 2 study covered under this award was established at three sites in Georgia during Period 3, at the end of which a total of 55 subjects had been enrolled, and 43 had finished study participation (Table 1). At the end of Period 4 enrollment has been completed.

		Subjects Enrolled			Subjects Completed			Total Complete Subjects	Required by Protocol	Percent Complete
		Start of Period	Added in Period	End of Period	Start of Period	Added in Period	End of Period			
Cohort 1	GMH	19	16	35	12	11	23	23	25	92.0% *
Cohorts 2 and 3	GMH	26	50	76	21	47	68	95	95	100%
	AMC	5	11	16	5	10	15			
	ARMC	5	7	12	5	7	12			
TOTAL		55	84	139	43	75	118	118	120	98.3% *

Table 1: The number of subjects who were enrolled in the study and who completed study participation during the 4th period.

**No further subjects could be enrolled into the cohort, so enrollment was considered completed.*

Subjects are considered to have completed study participation if they have at least two hours of analyzable NIRS data. During the current year 84 subjects were enrolled, producing 75 completed subjects, 11 in Cohort 1 and 64 in Cohorts 2 and 3. At the end of the study 139 subjects had been enrolled and 118 had completed study participation. Twenty-nine enrolled subjects did not complete study participation because they were determined to be screen failures after enrollment (47.6%), or they withdrew consent (38.1%) or were withdrawn (14.3%) before two hours of data could be collected.

Cohort 1 Subjects

Cohort 1 subjects serve as control subjects that are critically injured, but do not have any lower extremity injuries. They were recruited only at GMH. At the start of Period 4, 19 subjects had been enrolled into this Cohort, but only 12 had completed study participation. During Period 4 a protocol

amendment was made to increase the Cohort size from 25 to 35 to ensure we had the 25 completed subjects required of the protocol. However, we hit the new 35 enrollment limit on 08/20/2013 with only 23 completed subjects. This was considered sufficient subjects for the control cohort, so another protocol amendment to increase the sample size further was not considered.

Cohort 2 Subjects

Cohort 2 subjects are patients with tibia/fibula shaft or tibial plateau fractures that are caused by high-energy impacts and are therefore likely to develop ACS. The size of this cohort was also increased from 95 to 120 during the year to ensure 95 completed subjects were accrued according to our goal in the award proposal. This commitment was achieved in September with the completion of the 95th subject.

Cohort 3 Subjects

Cohort 3 subjects are Cohort 2 subjects that develop ACS and have a fasciotomy. In the original award proposal we estimated that about 25% of our high energy leg trauma subjects would develop ACS and transition into Cohort 3. We expected 25 Cohort 3 subjects to emerge from our 95 Cohort 2 subjects. However, this did not happen. Only eight cases of ACS resulting in fasciotomy were encountered.

2e: Analyze Data, Provider Feedback

We have evaluated all the NIRS data recordings for quality purposes, identifying instances where data is missing and correlating these instances against entries on the NIRS Monitoring Log that document the coordinators' experience with the NIRS devices and the patient's clinical history while on the study. The log is a meticulous record of events that happen that may cause a break in data collection, such as when the patient is moved, and information on recording quality reported by the NIRS device.

As part of some preliminary data analysis in the 2nd quarter of this year, data on the first 58 patients enrolled into Cohort 2 (those with traumatic leg injuries), was analyzed to determine if near infrared spectroscopy is able to accurately measure oxygenation in injured legs despite increased swelling, edema and various depths of fat. This analysis has been continued through the 3rd and 4th quarters and now includes 95 patients, 50 analyzable subjects.

Data cleaning, analysis and abstract / manuscript preparation for public presentation of study results will be undertaken in the time remaining in the overall grant period now that subject enrollment is complete. The amount of data collected in this study is enormous as it includes longitudinal NIRS measurements taken every 3 seconds for each patient over a 24 – 48 hour period. With data on the last few subjects yet to be sent to the CRO for entry and the mountain of analysis and interpretation before us, the completion of this task will necessitate a no-cost extension of the research study.

2f: Present and Publish Results of Phase 2 Study

Not due until completion of the Phase 2 study, planned for the second half of Year 4.

NIRS capabilities in the obese – NIRS is able to measure oxygenation to a depth of 2 to 3 cm below the skin, raising concerns over the ability of NIRS to accurately determine oxygenation of leg compartments in the obese. We collected data on 60 healthy participants. Our results indicated that NIRS was able to detect changes in oxygen saturation of muscle with exercise in all 60 participants

regardless of BMI. Even in the morbidly obese, depth of subcutaneous fat was less than 2cm in 98% of subjects (Figure 1). This data has been submitted for publication.

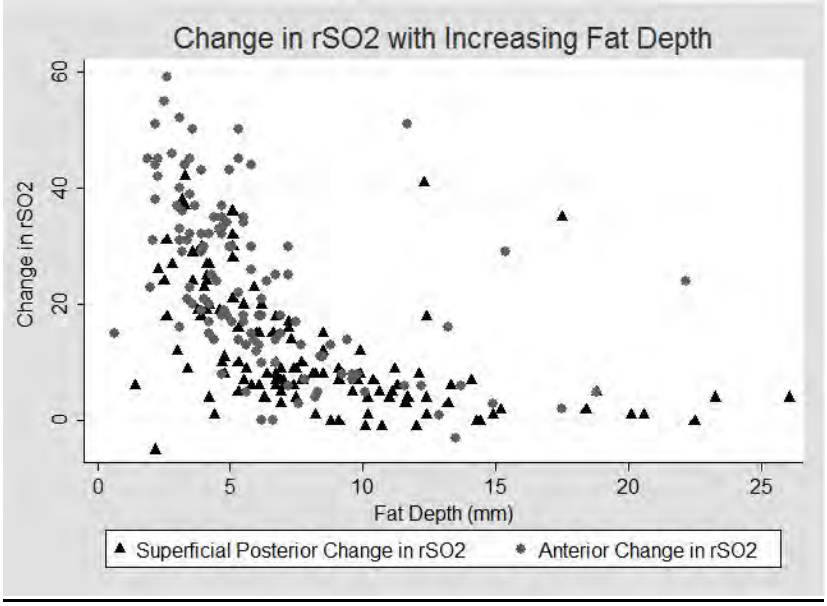


Figure 1: Change in oxygenation of muscle compartments with increasing depth of subcutaneous fat for anterior and superficial posterior leg compartments.

Subcutaneous depth in a traumatized lower extremity – In addition to obesity, concerns have also been raised about the ability of NIRS to accurately determine oxygenation of injured leg compartments in the presence of swelling and edema. We investigated these effects using data from 50 subjects in our Phase II trial with analyzable ultrasound fat-depth measurements. Results indicated that NIRS does have the ability to monitor muscle in injured extremities. There was no significant difference in subcutaneous depth between injured and uninjured legs (Table 2). All subjects had depths less than 2 cm. This data has been accepted for publication in the Journal of Trauma and Acute Care Surgery's Military Supplement. Please refer to the manuscript for more detailed description of the results.

Table 2: Mean difference in adipose tissue thickness (ATT) by injury type

Injury Type	N	Injured ATT Mean (sd)	Uninjured ATT Mean (sd)
Motor Vehicle Collision >15mph	19	7.92 (3.60)	6.93 (3.20)
Motor Vehicle Versus Pedestrian	11	6.01 (2.45)	6.46 (3.77)
Sports / Recreation	8	6.04 (2.32)	7.35 (2.43)
High Velocity Gunshot Wound	6	6.97 (3.99)	9.20 (4.68)
Fall >8ft	5	7.54 (3.08)	6.48 (2.93)
Crush Injury*	1	4.3	3.8
Total	50	6.98 (3.17)	7.06 (3.37)
*N=1; No standard deviation reported			

Skin pigment – The objectives of this study were to 1) collect descriptive data that will allow us to reach a more thorough understanding of factors that contribute to NIRS values and 2) to determine which of three commercially available NIRS devices are able to accurately provide a NIRS value in the presence of varying skin color (melanin and erythema). The three devices tested were the INVOS by Covidien, the Equanox by Nonin Medical, and the ForeSight by Casmed. Significant correlation of

skin pigment and oxygenation was found with the Covidien device, moderate with the Casmed device and no significant correlation detected with the Nonin device. Tables depicting the correlations can be seen in Tables 3a-b below. These results indicate that the Nonin device is the best at removing effects of skin pigmentation. A manuscript is currently being prepared for submission to the Journal of Biomedical Optics.

Table 3a

	Melanin	Erythema	Red	Green	Blue
INVOS	-0.4281**	-0.3647**	0.4262**	0.4230**	0.3970**
EQUANOX	-0.0574	0.0092	0.0259	0.0114	-0.0011
CASMED	-0.3514**	-0.2010**	0.3075**	0.2866**	0.2458*

Table 3b

	Melanin	Erythema	Red	Green	Blue
INVOS	-0.4900**	-0.0079	0.3390**	0.5079**	0.4971**
EQUANOX	-0.1342	-0.0638	0.1419	0.1406	0.1348
CASMED	-0.1376	-0.0086	0.1343	0.1489*	0.1323

Correlation of rSO_2 values and Skin Color by Device. Skin color measurements were taken using the DSM II ColorMeter (Cortex Technology, Hadsund, Denmark). (a)The average of three measurements for each subject's anterior leg compartment was tested for significant correlation with rSO_2 within each device. An * indicates significance at the 0.05 level, ** significance at α=0.01. (b) Correlations for the volar forearm were collected and analyzed identically to the anterior leg compartment.

Ambient Light – Through our research we hope to prove, among other points, that NIRS would be a valuable peri-operative tool for patients at risk of developing ACS. Here we investigated the effects of ambient light on the oxygenation readings from the same three commercially available NIRS devices. NIRS readings were recorded for 30 subjects at three different light levels: lights off, lights on, and over-head OR lights on. Significant problems in producing a reading were detected with both covidien and casmed, as they were unable to provide a value in the presence of too much light (OR lights on). It was found that there was no significant difference in oxygenation values displayed between the varying levels of light with the Nonin device. Casmed displayed no significant difference with lights on versus off, although the device was unable to display a reading when OR lights were turned on. Covidien, however, showed a significant difference between values when lights were off vs on (Diff of -0.933; p=0.0045) as well as when lights were off vs OR lights on (Diff of -5.0; p=0.0035).This manuscript is in its final stages of revision and will be submitted to the Journal of Biomedical Optics. A more detailed version of the analysis and results will be included in this manuscript.

TASK 3: Animal Use Study

Three porcine studies were planned for this project, two of which were completed on time in previous periods of this award. In the final quarter of Period 3 we began planning the last of the animal studies, in which we will evaluate the NIRS response to a "missed" compartment syndrome. This model uses NIRS to monitor the changes that take place when a fasciotomy is performed too late and muscle has died. This study was initiated in the 1st quarter of the 4th period under a no-cost extension at UGA. This third stage of testing received IACUC and ACURO approval in the 3rd quarter of this period. All 6 pigs (two groups of 3) were completed in this final quarter of period 4.

3a: Created UGA IACUC Protocol Application for Animal Studies

The protocol for the missed fasciotomy porcine study was developed during the first quarter of Period 4, in which we evaluated the NIRS response to a "missed" compartment syndrome. This model used

NIRS to monitor the changes that take place when a fasciotomy is performed too late and muscle has died. For the final 6 pigs, we induced trauma to recreate a leg injury, then increased intercompartmental pressure up to levels indicative of ACS for 8 hours via an albumin infusion. The 8 hour time period ensured that we would encounter dead muscle at the time of fasciotomy and allowed us to longitudinally monitor the transition from ischemic to dead muscle tissue.

3b: Obtain UGA IACUC and USAMRMC ACURO Approvals for Second Study
The protocol was approved by the UGA IACUC in the first quarter of Period 4, and by ACURO in the second quarter.

3c and d: Initiate and Conduct Animal Studies
In the third quarter of the fourth period the missed fasciotomy study was initiated and one animal had completed the protocol. The study was completed in the fourth quarter with a sample size of 6 animals.

3e and f: Analyze Data and Prepare for Presentation and Publication
The manuscript submitted in quarter 4 of year 3 to the Journal of Orthopedic Trauma has been accepted. As reported in the last quarter, the veterinary team is still in the process of writing a second manuscript pending additional assay results. The abstract entitled Evaluation of NIRS, serum biomarkers, and muscle damage in a porcine balloon compression model of acute compartment syndrome, was accepted and presented at MHSRS in August.

TASK 4: Reduction to Practice and FDA Approval Process

4a: Finalize product development relationships between Nonin, Inc and J+M Shuler – Completed in Year 2

4b: Begin reduction to practice process – Ongoing

4c: Produce final prototype for use in completion of Phase 1, all of Phase 2 and the investigational clinical study to be supported by a future grant – Ongoing
In our earlier annual reports, based on our experience to date at the time, we had declared that the NIRS technology is mature and ideal for our intended indication, and that we had the final prototype. However, in view of the missing signal errors we have encountered (documented in the Problem Areas section) in our Phase 2 clinical study completed this period, it is clear that there are some unexpected challenges to using NIRS on traumatized tissue. Some of the challenges were user related. The maturation of our research team into the world's leading users of NIRS technology in the setting of severe leg injury has allowed us to overcome many of the data acquisition issues; however, despite excellent and perfected technique, some issues remain in some patients regarding missing signal errors. In some injured muscle compartments there is increased absorption of NIR light such that the amount reflected back to the sensor falls below the sensor's sensitivity. Nonin developed a prototype sensor with larger photoreceptive diodes, which may mitigate this issue. There are also other modifications that could be made to the sensor to improve monitoring of rSO_2 in traumatized tissue, such as increasing NIR light emission. The 7600 oximeter itself fits the intended use; although increasing the number of ports per machine would be make it more functional.
4d: Respond to provider feedback re: functionality and industrial design – Completed
In our experience with the 7600 oximeter, the only two significant physical improvements needed are:

1. The addition of more ports to a machine, so that a patient can be monitored by a single machine, and

2. “horse-tailing” of leads, such that four (or more) sensors connect via a short cable (one foot) to a common trunk cable that runs to the device. This will cut down on the cable clutter in the current configuration that has led to subjects withdrawing from the study.

TASK 5: Coordination between study sites

5a: Bi-annual collaborators meeting – Ongoing
Given the transition from LRMC as a research site for the Phase 2 clinical study, to the Atlanta area, we have increased on-site visits to 3/year. On site visits during Period 3 include:

- 01 to 04 January 2013 – Site management
- 01 to 04 April 2013 – Site management
- 04 to 07 August 2013 – Site management and preparation for closeout

5b: Conduct weekly VTC (Telcon) for LRMC/J+M Shuler, and OIF/OEF during Phase 2 – No longer required since Phase 2 study is not being conducted in Georgia and not at LRMC.

5c: Rapid interpretation of weakness in the design and function of sequential NIRS pad prototypes and NIRS monitoring algorithms – Ongoing
The device is in a state where it is and has been fully ready for testing in our studies. It will probably undergo some minor physical improvements with time. The major improvement will be the design and validation of a diagnostic algorithm based on NIRS values. This process is ongoing and will continue past our grant period. This process will ultimately require validation in a prospective interventional trial.

5d: Coordinate response to FDA requests for information during approval process – Ongoing
LTC David Shoemaker, Marieann Brill and “Decision Gate” are all involved in USAMMDA’s sponsorship of this project and the creation/maintenance of an FDA compliant medical monitoring program for the three clinical sites in the Phase 2 study. As a result, this Phase 2 study will be permissible for inclusion in the “burden of proof” submission for our ultimately new FDA 510k approved indication.

5e: Insure mandatory reporting to SAMMC, ISR & USAMRMC is maintained – Ongoing and in good standing.

TASK 6. Future Research Endeavors
The main outcome of this task is to start the next step in the development and validation of NIRS for diagnosis of ACS. Based on results from the animal and clinical studies included under this award, clinical guidelines for the use of NIRS for the diagnosis and treatment of ACS will be developed and validated. The next step is to plan and conduct a prospective, clinical trial to calculate the sensitivity and specificity of NIRS to diagnose ACS using a series of comparative benchmarks. Over the current period we have designed this study. A BAA pre-proposal has been written and submitted to USAMRMC. We are hopeful for the continued funding and support needed to leverage the lessons learned to date.

PROBLEM AREAS

In our Period 3 Annual Report we disclosed that, in certain subjects or injured muscle compartments, the NIRS sensors were unable to pick up or maintain a signal that is usable by the Nonin 7600 oximeter. Throughout Period 4 we have focused on determining the nature of the problem and possible solutions, as documented in our quarterly reports. Our current theory is that there is increased absorption of NIR light in traumatized tissue, possibly due to leakage of hemoglobin, such that the amount of NIR light reflected back to the sensor falls below the sensor's sensitivity limits. During the first quarter we implemented use of the Nonin 7610 oximeter to capture raw NIR wavelength data from all eight leg compartments that could be evaluated by Nonin engineers. Baseline recordings were captured on all subjects, and additional recordings were taken if missing signal errors were encountered. In all cases, 7610 data was captured on all eight compartments to provide appropriate comparisons. Preliminary analysis of 7610 data confirmed that missing signal errors were associated with levels of reflected NIR light that were below the detection sensitivity of the sensor. Thus, the issue seems to be that low reflected light levels are compromising the existent technologies ability to monitor injured compartments on all patients. Strategies for increasing receptor sensitivity were tested at the end of the study with some favorable results. The physics of this technology is an absolute truth, and the physiological feasibility has been repeatedly born out in our animal testing and human control subjects. The issues are engineering a platform that is robust enough to monitor all injured compartments. We are much closer today that at any point in the history of NIRS technology use in the detection of ACS.

In the third quarter Nonin developed a strategy to mitigate the missing signal errors due to low reflected NIR levels and to increase the quantity of engineering data that could be mined in these situations. They constructed a prototype sensor with larger photoreceptive diodes, and subsequently manufactured a batch of 50 "lemur" sensors (so called due to their visual and functional resemblance to the endemic Malagasy primates). Once available, Lemur sensors were used on the four subjects, in whom missed signal errors occurred, prior to the closure of this study. This data is still be analyzed.

KEY RESEARCH ACCOMPLISHMENTS

1. Completed the Phase 2 study as outlined in the protocol and original grant proposal:
    - Cohort 1 – 23 subjects completed (out of 25 – 92% complete)
    - Cohorts 2 and 3 – 95 subjects completed (100%)

2. Fourth animal study completed

3. One manuscript prepared.

4. Four conference abstracts submitted

REPORTABLE OUTCOMES

Manuscripts

1. Cathcart C, Shuler M, Freedman B, Reno L, Budsberg S. Correlation Of Near Infrared Spectroscopy (NIRS) And Direct Pressure Monitoring In An Acute Porcine Compartmental Syndrome Model. Journal of Orthopedic Trauma. July 2013.
2. Roskosky M, Robinson G, Reisman W, Ziran B, Shuler M, Freedman B. Subcutaneous Depth in a Traumatized Lower Extremity. Journal of Trauma and Acute Care Surgery. (In-press)

Abstracts

1. Roskosky M, Robinson G, Shuler M, Freedman B. *Subcutaneous Depth in a Traumatized Lower Extremity.* Society of Military Orthopedic Surgeons 55th Annual Meeting, December 2013. (Podium)

2. Budsberg S, Shuler M, Freedman B, Hansen M, Roskosky M. Evaluation of NIRS, serum biomarkers and muscle damage in a porcine balloon compression model of acute compartment syndrome. Military Health System Research Symposium (MHSRS), August 2013, Fort Lauderdale, FL (Poster)

3. Roskosky M, Robinson G, Shuler M, Freedman B. *Subcutaneous Depth in a Traumatized Lower Extremity.* Military Health System Research Symposium, August 2013. (Podium)

4. Roskosky M, Robinson G, Shuler M, Freedman B. *Subcutaneous Depth in a Traumatized Lower Extremity.* Southern Orthopedic Association 30th Annual Meeting, July 2013. (Poster)

CONCLUSIONS

The Phase 2 clinical study was completed during the fourth period. Eleven Cohort 1 subjects and 64 Cohort 2 subjects completed study participation during the year. Enrollment terminated at the end of the fourth period with 23 Cohort 1 subjects and 95 Cohort 2 subjects having completed the study, thus meeting our commitment under this award. The fourth porcine study was also completed during the fourth period.

The major tasks under this award have been completed. The remaining tasks, including data analysis, manuscript preparation, and presentation of results, will begin during the remainder of the performance period (which terminates at the end of calendar year 2013) and will require a no-cost extension for completion.

Our initial expectation of having a final prototype of an FDA-approved monitoring device with solid basic scientific and initial clinical research support as a diagnostic tool for ACS has been achieved. We complete Period 4, prepared to start and complete the final phase of this initiative. Unexpected challenges associated with continuous rSO_2 monitoring in traumatized muscle compartments have been confronted and most of been overcome. Preliminary data on the absorption and reflection of the NIR light in traumatized muscle that was captured during our Phase 2 study will begin to be analyzed over the final quarter of this award. This analysis will provide more information on the missing signal errors, and may lead to sensor design modifications to mitigate the errors. A full description of the missing signal errors and our strategy to understand and mitigate the errors will be presented in the Final Report for this award.

Journal of Orthopaedic Trauma Publish Ahead of Print
DOI: 10.1097/BOT.0b013e3182a75ceb

Correlation of near infrared spectroscopy (NIRS) and direct pressure monitoring in an acute porcine compartmental syndrome model

Curtis C. Cathcart, DVM[1], Michael S. Shuler, MD[1,2], Brett A. Freedman, MD[3]5 , Lisa R. Reno,
BS[1], Steven C. Budsberg DVM, MS[1]6 .

[1] Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA
[2]10 Department of Upper Extremity and Micro Surgery, Athens Orthopedic Clinic, PA, Athens GA
[3]11 Landstuhl Regional Medical Center, Landstuhl, Germany
Corresponding Author – Dr. Steve Budsberg Department of Small Animal Medicine and Surgery College of Veterinary Medicine University of Georgia, Athens, GA 30602
Phone: 706-206-7585 Fax : 706-542-6460 Email: Budsberg@uga.edu

Steven C. Budsberg received money from the following pharmaceutical companies for consulting efforts and funding of research projects (Pfizer, Merial, Eli Lilly and Novartis.) Michael S. Shuler: Intellectual property and licensing agreement for IP with Nonin Medical, Inc.
Funding: **DR080018**: *Near- Infrared Spectroscopy to Reduce the Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Solders Injured in OEF/OIF*.

Department of Defense (DOD) Deployment Related Medical Research Program (DRMRP) of the Office of the Congressionally Directed Medical Research Programs (CDMRP)

The authors have no conflicts of interest to declare.

Objective: To correlate near infrared spectroscopy (NIRS) and the tibial intra-compartmental perfusion pressure (TIPP) in an acute limb compartmental syndrome (ALCS).

Methods: Landrace swine subdivided into 2 groups, plasma infusion (N=16) and blunt trauma plus plasma infusion (N=15). NIRS sensors were placed over the craniolateral muscle compartment of proximal both tibiae. Albumin infusion elevated tibial intra-compartmental pressures (TICP). Time synchronized measures of systolic (SAP), diastolic (DAP) and mean pressures (MAP), TICP, and percent oxygenation from each leg were collected. For the blunt trauma group, trauma was induced by dropping a 2kg weight 30 times from100 cms directly on the muscle compartment. For each group, a repeated measures ANOVA model was used to test differences in TICP, TIPP and oxygenation values. Pearson's correlations were calculated between TICP and oxygenation, and TIPP and oxygenation.

Results: Both models created reproducible increases in TICP and decreases in TIPP. Trauma did not alter TICP, TIPP or percent oxygenation in the model. NIRS was able to detect significant changes in tissue oxygenation at all the same time points. NIRS was able to detect decreased oxygenation at every TIPP decrease and subsequent increase following fasciotomies. An increase in percent oxygenation was seen in all cases once fasciotomy was performed and TICP was reduced.

Conclusions: NIRS provided a sensitive measure correlating to both an increase and decrease in TICP and TIPP, respectively, in this infusion model. The addition of blunt trauma to the model did not alter the correlations of NIRS values with TICP and TIPP. Fasciotomy produced a rebound in oxygenation values.

Key words: Compartmental Syndrome;Porcine Model;Near Infrared Spectroscopy

Introduction

Over the last two decades, tissue oxygenation saturation (StO_2) measured by near infrared spectroscopy (NIRS) has been extensively evaluated for use in determining systemic and regional tissue perfusion (1-4). It is widely used, and validated for monitoring cerebral oxygenation during anesthesia (5-7). Recent efforts have focused on this use of NIRS in assessing regional perfusion and more specifically regional perfusion in the setting of acute limb compartmental syndrome [ALCS] (8-11). Current objective measures of compartment health in ALCS focus on intra-compartmental pressure, as a proxy for perfusion of the tissue (12-14). The invasive measurement of pressure within the limb compartment in question provides indirect data on the physiological state of the limb compartment (9). This technique has been used for decades and recommendations for fasciotomy (the universally accepted treatment for ALCS) exist that are based upon both absolute intra-compartmental pressure (ICP) and differential pressure (perfusion pressure or PP) [diastolic arterial pressure – ICP] (12-15). While either mean arterial pressure or diastolic blood pressure could be used as the perfusion technique, diastolic pressure seems to be a more reliable measure (16,17) Animal and human studies have explored different aspects of ACLS as well as a variety of NIRS setting for potential use in ALCS (13,16-25). Studies have suggested when PP drops below 20 to 10 mmHg tissue ischemia occurs and justifies fasciotomy (16,17, 26) Correlating continuous NIRS monitoring of the compartment with PP may help guide clinicians with treatment decisions as well as creating prognostic data via StO_2 measurements. Two studies in a porcine model of ALCS in the proximal craniolateral tibial compartment showed correlations of ICP with oxygenation, and documentation of significantly different levels of StO_2 measured by NIRS in hypotension, hypotension and

hypoxeia (with and without increased ICP) respectively(18,19). In each study ALCS was defined as a loss of muscle twitch during peroneal nerve stimulation but interestingly mean ICP varied greatly. Neither study found an ICP predictive of muscle twitch cessation and furthermore there is no data suggesting that either absolute ICP or PP values indicated reversible or irreversible tissue injury in the limb compartment. Additionally, none of the research or clinical models to date have addressed the potential concerns of NIRS measurement variability in the presence of trauma induced tissue edema or hemorrhage.

The goal of this study was to correlate ICP and PP with percent oxygenation through a wide range of ICP and PP values in an acute porcine model and to determine if blunt force trauma to the limb would alter these correlations using a commercially available NIRS device. The hypotheses tested were that ICP and PP would have correlations with percent oxygenation throughout a wide range of pressures and that acute blunt force trauma would not alter oxygenation values or the associated correlations with compartment pressures.

Materials and Methods

Animals – Thirty one landrace swine (48-68 kg, 16 males, 15 females) were used in the study (IACUC # A2010 1-012).

Study Design – Pigs were divided into two experiments. Experiment 1 was a plasma infusion model (group 1) of 16, and the second experiment was the blunt trauma component completed prior to the same plasma infusion (group 2) of 15 animals. All pigs underwent the same experimental procedures and monitoring setup as described herein. Pigs were maintained on isoflurane (IsoFlo®**,** Abbott Laboratories, North Chicago, IL 60064 USA) with mechanical positive pressure ventilation. A circulating warm water pad maintained rectal body temperatures

between 98 and 101 degrees Fahrenheit. A 20 gauge intravenous catheter was placed in an auricular vein for constant infusion of lactated ringer's solution (Veterinary Lactated Ringer's Injection USP, Abbott Laboratories, North Chicago, IL 60064) at 5 ml/kg/hr. Pigs were positioned in dorsal (supine) recumbency. Surgical cut downs exposed a median femoral artery for direct arterial pressure measurement, and the right jugular and femoral vein for blood sampling of the test leg via 18 gauge catheters. Both hind limbs (from stifle to tarsus) were clipped of hair, cleaned with 4% chlorhexidine scrub (2% Chlorhexidine Gluconate, First Priority Inc., Eglin, IL 60123-1146) and alcohol (70%). NIRS self-adhesive sensors (EQUANOX^{TM} Sensor, Model 8003CA, Nonin Medical, Inc., Plymouth, MN) were placed on the skin overlying the muscles of the craniolateral compartment of each leg (i.e. test and control legs of both the plasma infusion and blunt groups), such that at least 1 cm of craniolateral compartment musculature extended proximal, cranial and caudal to the sensor. On the test leg, four 18 gauge needles were placed at the periphery, centered on each side of the sensor and angled 20 degrees toward the center of their tips were in the field monitored by the NIRS sensor (Figure 1). The proximal and distal needles were attached via a T-connection for infusion of 5% human albumin (AlbuRx^{TM} 5, CSL Behring AG, Bern, Switzerland) to manually elevate the compartmental pressure at predetermined intervals in the test legs. The cranial and caudal needles were used for direct pressure transducer measurement of compartmental pressure by averaging the values. On the control legs, a single 18 gauge needle was placed on the lateral aspect of the NIRS sensor for direct pressure transducer measurement of compartmental pressure (intermittently flushed to assure patency and accurate readings). Continual time synchronized measurements of systemic blood pressure – systolic (SAP), diastolic (DAP), and mean pressures (MAP), pulse rate, respiratory rate, systemic pulse oximetry, body temperature,

compartmental pressures (2 transducers on test leg (averaged) and one on control leg), and regional oximetry (NONIN EQUANOX™ 7600 Oximeter, Nonin Medical, Inc., Plymouth, MN) from the NIRS sensors from each leg were collected. Once compartmental transducers were zeroed, tibial intra-compartmental perfusion pressure (TIPP) of the test leg was increased in increments by albumin infusion. Measurements were taken at baseline (0 mm Hg) for 10 minutes, TIPP of 40 mm Hg for 5 minutes, TIPP of 30 mm Hg for 5 minutes, TIPP of 20 mm Hg for 5 minutes, TIPP of 10 mm Hg for 5 minutes, TIPP of 0 mm Hg for 10 minutes, TIPP equal to MAP for 10 minutes, TIPP equal to SAP for 10 minutes and TIPP equal to SAP + 10 mm Hg for ten minutes. TIPP was calculated by subtracting ICP from diastolic pressure. At this time fasciotomies were performed and measurements taken for an additional 10 minutes. The first fasciotomy was performed by sharp incision caudolateral of the NIRS sensor from stifle to hock to a depth through fascial layers of the muscular compartment. If there was not an immediate (within 60 seconds) increase in percent oxygenation, a second fasciotomy was performed in a similar manner along the craniolateral aspect of the tibia.

The blunt trauma group of 15 pigs was maintained on isoflurane with mechanical positive pressure ventilation using an identical protocol as the plasma infusion group. NIRS sensors were placed over the craniolateral compartment of each hindlimb in all animals as described above.. The continuous time-synchronized measures, as in the plasma infusion group, were recorded for both legs for 10 minutes to establish baseline. After equilibration, the location of the 18 gauge needles and NIRS sensor on the leg was outlined and the instrumentation removed. The craniolateral musculature on the test leg was then traumatized in the following manner: the craniolateral compartment was positioned by slightly internally rotating the test hind limb which was held in place using an Olympic Vac-Pac® patient positioning system. Once placed around

the leg, this system became rigid when vacuum was applied, effectively holding the leg in a stable position until trauma induction was complete. Next a 2 kg weight was dropped down a vertically orientated cylindrical tube 30 times from a 100 cm height. A plumb bob attached to the outside ensured the apparatus was vertical for each drop. The measurement instrumentation was replaced on the test leg within the previously outlined area immediately after trauma induction and a 45 minute equilibration period was recorded before start of colloid infusion (5% human albumin). The contralateral leg was used as an internal control and was not traumatized. An identical testing protocol including increasing intra-compartmental pressure and monitoring was performed. All pigs were euthanized at the end of the experiment with an intravenous injection of pentobarbital sodium (Beuthanasia® –D Special, Schering-Plough Animal Health Corp., Union, New Jersey 07083). Total time of altered TIPP was 70 minutes.

Statistical Analysis - A repeated measures model that recognized multiple observations was used to test for differences in tibial intra-compartmental pressure (TICP), TIPP and oxygenation values between test and control limbs and time points in both groups. The full model included factors for group, time point and a group by time point interaction. Multiple comparisons were adjusted for using Tukey's test. All hypothesis tests were 2-sided and the significance level was $\alpha = 0.05$. Pearson's correlations were calculated between TICP and percent oxygenation measurements and between TIPP and percent oxygenation.

Results

In both experimental groups (plasma infusion and blunt trauma plus infusion), there was consistent, reproducible increases in TICP and decreases in TIPP (Figures 2-5). No significant

differences in TICP, TIPP or percent oxygenation were seen between plasma infusion and blunt trauma groups at all time periods during the experiment. Significant increases in TICP between test and control limbs were found at all time points except TIPP=40mmHg and 5 and 10 minutes following fasciotomies. NIRS was able to detect significant changes in tissue oxygenation at all the same time points. All TICP of the test leg increased significantly from baseline except for 10 minutes following fasciotomy. Once TIPP reached 20mmHg, oxygenation decreased significantly from baseline and did not return to baseline levels until 5 to 10 minutes after fasciotomies (Figures 3&5). NIRS was able to detect decreased oxygenation at every TIPP decrease and subsequent increase following fasciotomies. TIPP was significantly different than baseline at all time points until 5 minutes after fasciotomies. Similar TIPP and TICP were observed among plasma infusion and blunt trauma test limbs, with the exception that blunt trauma test limb oxygenation values were significantly lower immediately after the trauma event. Significant negative correlations of TICP and percent oxygenation (trauma: $r= -0.74$, $p<0.0001$; plasma infusion: $r=-0.79$, $p<0.0001$) and positive correlations of TIPP and percent oxygenation (trauma: $r=0.76$, $p<.0001$; plasma infusion: $r=0.80$, $p<0.0001$) were observed.

In both groups, the initial caudolateral fasciotomy was performed by sharp incision caudolateral to the NIRS sensor from stifle to hock to a depth through all fascial layers of the muscular compartment. When performing fasciotomies, no pig had a depth greater than 5mm of subcutaneous fat, well within the known limits of the NIRS device. In the plasma infusion group, seven pigs did not have an immediate increase in percent oxygenation and a second fasciotomy was performed to restore pressures to normal levels (Table 1). Similarly, in the blunt trauma group eleven pigs received a second fasciotomy. Once a second fasciotomy was performed, the oxygenation levels normalized as the pressure normalized. Thus NIRS was able to detect

decreased tissue oxygenation at every perfusion pressure decrease and subsequent increase following pressure relieving fasciotomies. TIPP pressures were significantly different than baseline at all time points until 5 minutes after fasciotomies. Despite 70 minutes where perfusion pressures were significantly below baseline, tissue oxygenation returned to normal values after compartmental pressure release (Figure 5).

Discussion

The current data supported the hypotheses tested in the study. NIRS had significant correlations to both ICP and PP throughout a wide range of pressures in the tibial muscle compartment. Additionally NIRS was not altered by the addition of acute blunt force trauma to the model or the associated correlations with compartment pressures. These results confirm that NIRS can provide a viable real time method of longitudinal sampling of assessing regional perfusion and more specifically regional perfusion in the setting of acute limb compartmental syndrome. These data provide new insight into this relationship as previous articles had no correlation to PP since synchronized measurements with systemic blood pressure were absent and PP could not be calculated (16,17). The lack of change in NIRS values for the trauma group contrasts a finding of Shuler et al (20) in which in a series of tibial fracture cases showed increased NIRS values peripheral to the fracture site. The difference between these results may be due to the mode and severity of limb trauma and exact sites measured. In this model, NIRS values were measured only directly over the traumatized tissue and not peripherally as was done previously.

Data from this study suggests that NIRS may have a role in determining a threshold level of a specific outcome measure that can assist the clinician's decision whether or not to perform a fasciotomy. It was noted that NIRS values dropped significantly from baseline at a TIPP of 20 mm Hg or less in both the plasma infusion and blunt trauma test limbs. Thus, NIRS is able to detect differences in oxygenation at TIPP considered to be diagnostic for ALCS and a threshold for fasciotomy (16, 17) . While these data do not suggest nor document any effect on the muscle tissue, they do provide evidence for a future avenue of work.

The data involving the fasciotomies also provided some interesting results. While there is no way to know if the limbs that did receive a second fasciotomy would have had improved PP and higher NIRS values over time without the second fasciotomy, the NIRS provided real time data that could be used to assess if the initial fasciotomy was successful in releasing intra-compartmental pressure and restoring muscle perfusion. NIRS was 100% sensitive and specific to determining an incomplete release of intra-compartmental pressure in this limited study. This finding has implications as a potential use of NIRS intra-operatively as a quality control device to insure adequate release of the compartments to prevent insufficient releases (15).

A second finding was that in limbs of both pigs groups where a second fasciotomy was performed, TIPP could improve toward baseline initially without a NRIS change up to a certain point. As shown in the results during this time, the NIRS was not changing and thus the decision to perform the second fasciotomy was made. While current data documents there is a direct relationship of TIPP to NIRS, the NIRS values may be more sensitive in the initial attempts at compartmental decompression as it assesses the tissue oxygenation and not merely an arbitrary change in pressure.

A second point of potential difference between current data and previous studies using this model exists (16, 17). Landrace pigs used in the current study were larger (40 to 45 kgs) and allowed for measurement of a tibial compartment with depths to 25 millimeters. Previous studies (16, 17) used smaller Landrace pigs (13 to 18kgs); pigs of similar size had measured tibial compartments size with depths of 8-12 mm. Given the fact that the sensor is calibrated over a 25 millimeters depth, it is possible there was tissue averaging affecting the results of the previous studies. The sensors in our study should be sampling from the affected compartment alone.

One limitation of this study and previous studies (16, 17) was the model chosen to represent ALCS. The infusion of 5% albumin was used to mimic effusive conditions of trauma as well as provide a means to increase compartment pressure in a controlled fashion. The model does not take into account the inflammatory response seen with ALCS, and in the trauma group, may not represent the same inflammatory and vascular response as well as soft tissue trauma seen in ALCS. With potentially different underlying pathology, the fasciotomy may have different effect in ALCS compared to this model.

An additional limitation was the use of straight needles to measure ICP. Needles have a tendency to plug when inserted into muscle, and the use of side ports may have prevented a potential issue with needle plugging. However, the two needle system was designed with two measurements to ensure accurate values. Needles were cleared of plugs after insertion and filtrated periodically (approximately every 2-3 minutes) thereafter.

In both blunt trauma and plasma infusion groups a positive correlation was seen between tissue oxygenation as measured by NIRS and with TIPP while TIPP was above 0 mm Hg. The

fall of TIPP below this critical level of 0 mm Hg caused significant drop of detectable tissue oxygenation yet progressively lower TIPP beyond this was not related to progressively lower tissue oxygenation as measured by NIRS. Likewise as TIPP increased after fasciotomy, initial increase was not correlated with increasing tissue oxygenation until this critical level was surpassed at which time NIRS values and TIPP regained a positive correlation. These findings may help to define where the threshold for ischemia occurs with PP (0 mm Hg) which is consistent with early studies (18, 25). These findings support the theory of PP playing a critical role in the development of ALCS.

The current data confirms that NIRS monitoring can provide important real time diagnostic information on tissue oxygenation in the face of potential ALCS as well as feedback on treatment endpoint measures for fasciotomy. Furthermore, NIRS is responsive to perfusion changes as they occur prior to any permanent muscle damage.

262

263 **References**

264 1. Hamaoka T, McCully KK, Quaresima V, et al. Near-infrared spectroscopy/imaging for
265 monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. J
266 Biomedical Optics 2007;12: J Biomed Opt. 2007;12:062105. PMID: 18163808
267 2. Hamaoka T, McCully KK, Niwayama M, et al. The use of muscle near-infrared
268 spectroscopy in sport, health and medical sciences: recent developments. Philos Transact A Math
269 Phys Eng Sci. 2011;28:4591-604. PMID: 22006908.
270 3. Scheeren TW, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared
271 spectroscopy (NIRS): background and current applications. J Clin Monit Comput. 2012 Mar 31.
272 [Epub ahead of print]:PMID: 22467064.
273 4. Ward KR, Ivatury RR, Barbee RW, et al. Near infrared spectroscopy for evaluation of the
274 trauma patient: a technology review. Resuscitation 2006;68:27-44. PMID: 16325319.
275 5. Fadel PJ, Keller DM, Watanabe H, et al. Noninvasive assessment of sympathetic
276 vasoconstriction in human and rodent skeletal muscle using near-infrared spectroscopy and
277 Doppler ultrasound. J Appl Physiol. 2004;96:1323-30. PMID: 14657045.
278 6. Kim MB, Ward DS, Cartwright CR, et al. Estimation of jugular venous O2 saturation
279 from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. J Clin Monit Comput.
280 2000;16:191-9. PMID: 12578103
281 7. Mancini DM, Bolinger L, Li H, et al. Validation of near-infrared spectroscopy in
282 humans. J Appl Physiol. 1994;77:2740-7. PMID: 7896615.

8. Cole AL, Herman RA Jr, Heimlich JB, et al. Ability of near infrared spectroscopy to measure oxygenation in isolated upper extremity muscle compartments. J Hand Surg Am. 2012;37:297-302. PMID: 22189186.

9. Gentilello LM, Sanzone A, Wang L, et al. Near-infrared spectroscopy versus compartment pressure for the diagnosis of lower extremity compartmental syndrome using electromyography-determined measurements of neuromuscular function. J Trauma. 2001;51:1-9. PMID: 11468459.

10. Giannotti G, Cohn SM, Brown M, et al. Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. J Trauma. 2000 ;48:396-401. PMID: 10744275.

11. Gourgiotis S, Villias C, Germanos S, et al. Acute limb compartment syndrome: a review. J Surg Educ. 2007;64:178-86. PMID: 17574182.

12. Masquelet AC. Acute compartment syndrome of the leg: pressure measurement and fasciotomy. Orthop Traumatol Surg Res. 2010;96:913-7. PMID: 2093493.

13. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. J Bone Joint Surg Br. 1996;78:99-104. PMID: 8898137.

14. Olson SA, Glasgow RR. Acute compartment syndrome in lower extremity musculoskeletal trauma. J Am Acad Orthop Surg. 2005;13:436-44. PMID: 16272268.

15. Ritenour AE, Dorlac WC, Fang R, et al. Complications after fasciotomy revision and delayed compartment release in combat patients. J Trauma. 2008;64:S153-6. PMID: 18376159

16.. Heckman MM, Whitesides TE, Grewe SR, et al. Histologic determination of the ischemic threshold of muscle in the canine compartment syndrome model. J Orthop Trauma. 1993;7:199-210. PMID: 8326422

17. Matava MJ, Whitesides TE, Seiler JG, et al. Determination of the compartment pressure threshold of muscle ischemia in a canine model. J Trauma. 1994 ;37:50-8. PMID: 8028059.

18. Garr JL, Gentilello LM, Cole PA,et al. Monitoring for compartmental syndrome using near-infrared spectroscopy: a noninvasive, continuous, transcutaneous monitoring technique. J Trauma. 1999 Apr;46:613-6. PMID: 10217223.

19. Arbabi S, Brundage SI, Gentilello LM. Near-infrared spectroscopy: a potential method for continuous, transcutaneous monitoring for compartmental syndrome in critically injured patients. J Trauma. 1999;47:829-33. PMID: 10568708.

20. Cole AL, Herman RA Jr, Heimlich JB, et al.Ability of near infrared spectroscopy to measure oxygenation in isolated upper extremity muscle compartments. J Hand Surg Am. 2012 ;37:297-302. PMID: 22189186.

21. Shuler MS, Reisman WM, Cole AL, et al. Near-infrared spectroscopy in acute compartment syndrome: Case report. Injury. 2011;42:1506-8. PMID: 21489528.

22. Shuler MS, Reisman WM, Kinsey TL, et al. Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. J Bone Joint Surg Am. 2010;92:863-70. PMID: 20360509.

23. Shuler MS, Reisman WM, Whitesides TE et al. Near-infrared spectroscopy in lower extremity trauma. J Bone Joint Surg Am. 2009;91:1360-8. PMID: 19487513.

24. Whitesides TE, Heckman MM. Acute Compartment Syndrome: Update on diagnosis and treatement. J Am Acad Orthop Surg 1996;4:209-218. PMID: 10795056.

25. Whitesides TE, Haney TC, Morimoto K, et al. Tissue pressure measurements as a determinant for the need of fasciotomy. Clin Orthop Relat Res. 1975;113:43-51.PMID: 1192674

26. Clayton JM, Hayes AC, Barnes RW. Tissue pressure and perfusion in the compartment syndrome. J Surg Res. 1977;22:333-9. PMID: 850397

Figure Legends

Figure 1: Depiction of instrumentation for NIRS and direct pressure monitoring

A and C = Albumin infusion (5% human albumin)

B and D = Direct pressure transducer measurement of compartmental pressure

E = NIRS sensor

**Fasciotomy incisions are indicated by the red lines located (on the image) to the left and right of NIRS sensor (E). The incision to the left represents the craniolateral fasciotomy (fasciotomy 1) and the incision to the right represents the caudolateral fasciotomy (fasciotomy 2).

Figure 2a: Tibial Intracompartmental Pressure (TICP) and NIRS reported over time for plasma infusion group. N =16 ± SEM

Left Y-axis: TICP

Right Y-axis: Percent of oxygenated hemoglobin

s: start of each period, e: end of each period

MAP = mean arterial blood pressure

346 SAP = systolic blood pressure

347 SAP+10 = systolic blood pressure + 10 mm Hg

348 fasc 1: caudolateral fasciotomy, fasc 2: craniolateral fasciotomy

349 Long dash from fasc 1 to fasc+5 represents data from pigs that did not have a second fasciotomy.

350

351 Figure 2b: Tibial Intracompartmental Perfusion Pressure (TIPP) and NIRS reported over time

352 for plasma infusion group. . N =16 ± SEM

353 Left Y-axis: TICP

354 Right Y-axis: Percent of oxygenated hemoglobin

355 see Figure 2 key

356

357 Figure 3a: Tibial Intracompartmental Pressure (TICP) and NIRS reported over time for the blunt

358 trauma group. . N =15 ± SEM

359 Left Y-axis: TICP

360 Right Y-axis: Percent of oxygenated hemoglobin

361 See Figure 2a key - PT equil: post trauma equilibration period

362

Figure 3b: Tibial Intracompartmental Perfusion Pressure (TIPP) and NIRS reported over time for the blunt trauma group. . N =15 ± SEM

Left Y-axis: TICP

Right Y-axis: Percent of oxygenated hemoglobin

See Figure 3a key

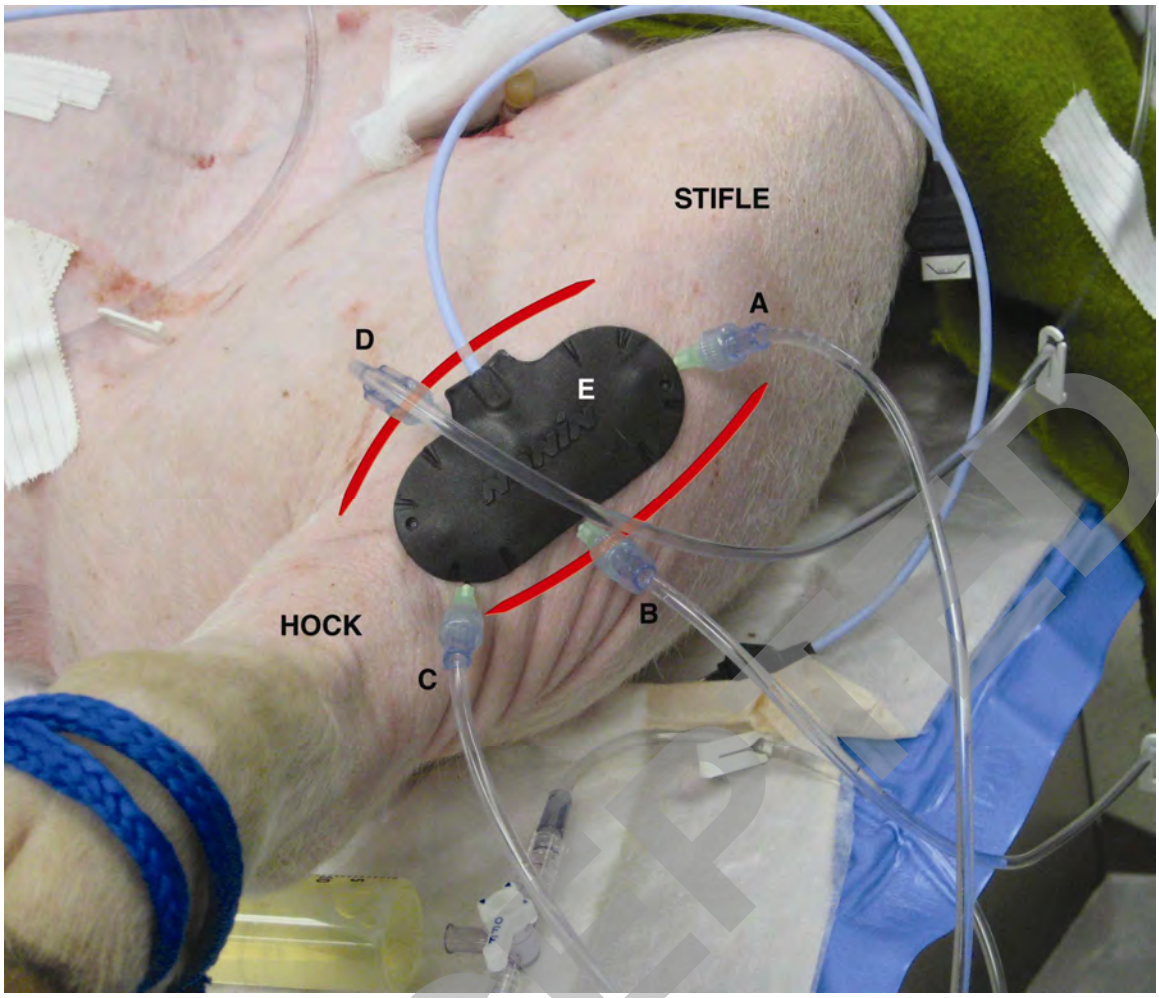
Table 1: NIRS and perfusion pressures for the first 60 seconds after each fasciotomy for the two groups. This is data not included in figures 1-4. Mean ± SEM

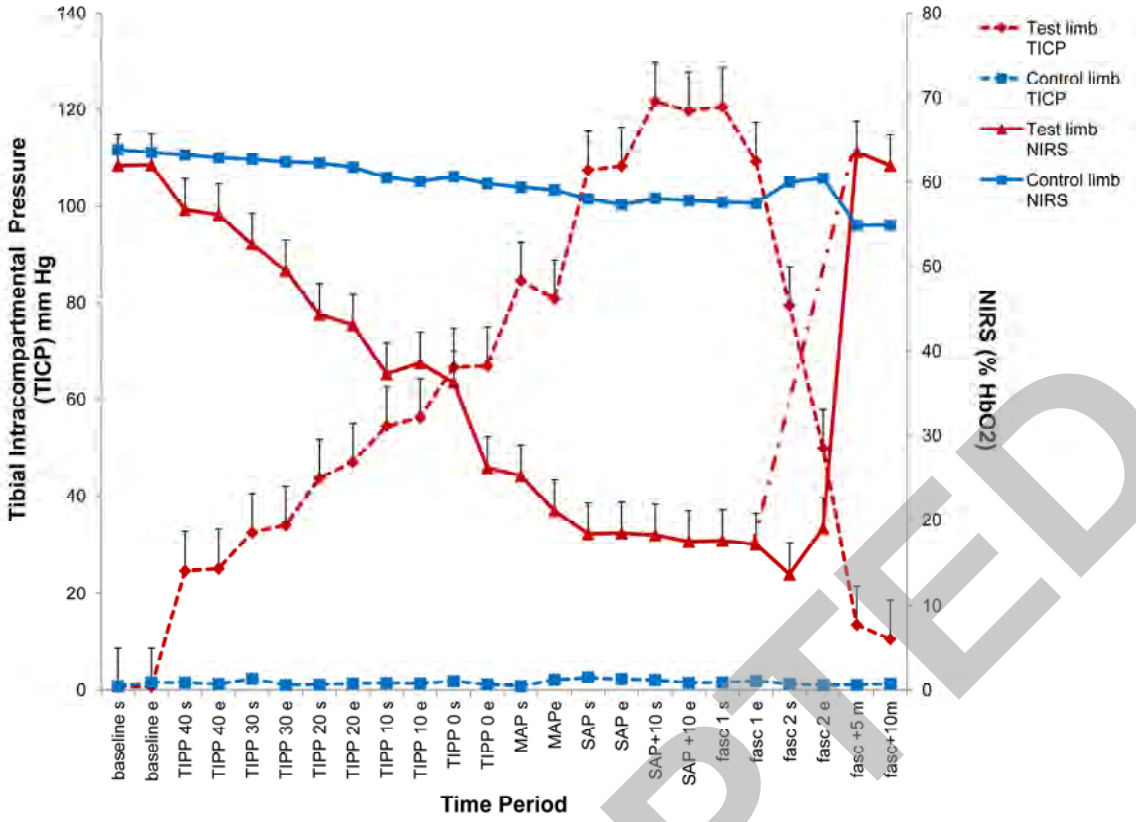
Control	Fasciotomy (1) n = 9		Fasciotomy (2) n = 7	
	NIRS Value	**Perfusion Pressure**	**NIRS Value**	**Perfusion Pressure**
Pre-first fasciotomy	23.8 ± 3.3	-49.0 ± 4.2	16.3 ± 0.2	-46.8 ± 10.0
30 seconds post 1st fasciotomy	24.5 ± 4.5	-16.4 ± 15.1	17.0 ± 0.0	-37.9 ± 12.2
60 seconds post 1st fasciotomy	40.2 ± 6.0	34.9 ± 6.3	18.5 ± 2.5	-26.6 ± 9.3
Post-2nd second fasciotomy				
30 seconds post 2nd fasciotomy	NA	NA	21.5 ± 5.8	35.6 ± 4.4
60 seconds post 2nd fasciotomy	NA	NA	35.8 ± 10.3	43.9 ± 3.6
Acute Trauma	**Fasciotomy (1) n = 4**		**Fasciotomy (2) n = 11**	
	NIRS Value	**Perfusion Pressure**	**NIRS Value**	**Perfusion Pressure**
Pre-first fasciotomy	24.7 ± 0.3	–52.1 ± 11.7	22.5 ± 2.1	-58.9 ± 6.9
30 seconds post 1st fasciotomy	35.0 ± 11.0	1.7 ± 36.2	23.5 ± 1.4	-36.4 ± 6.7
60 seconds post 1st fasciotomy	41.5 ±13.5	9.35 ± 17.7	21.7 ± 1.0	-5.86 ± 8.1
Post-2nd second fasciotomy				
30 seconds post 2nd fasciotomy	NA	NA	31.5 ± 6.3	33.6 ± 6.7
60 seconds post 2nd fasciotomy	NA	NA	43.1 ± 9.8	46.1 ± 4.2

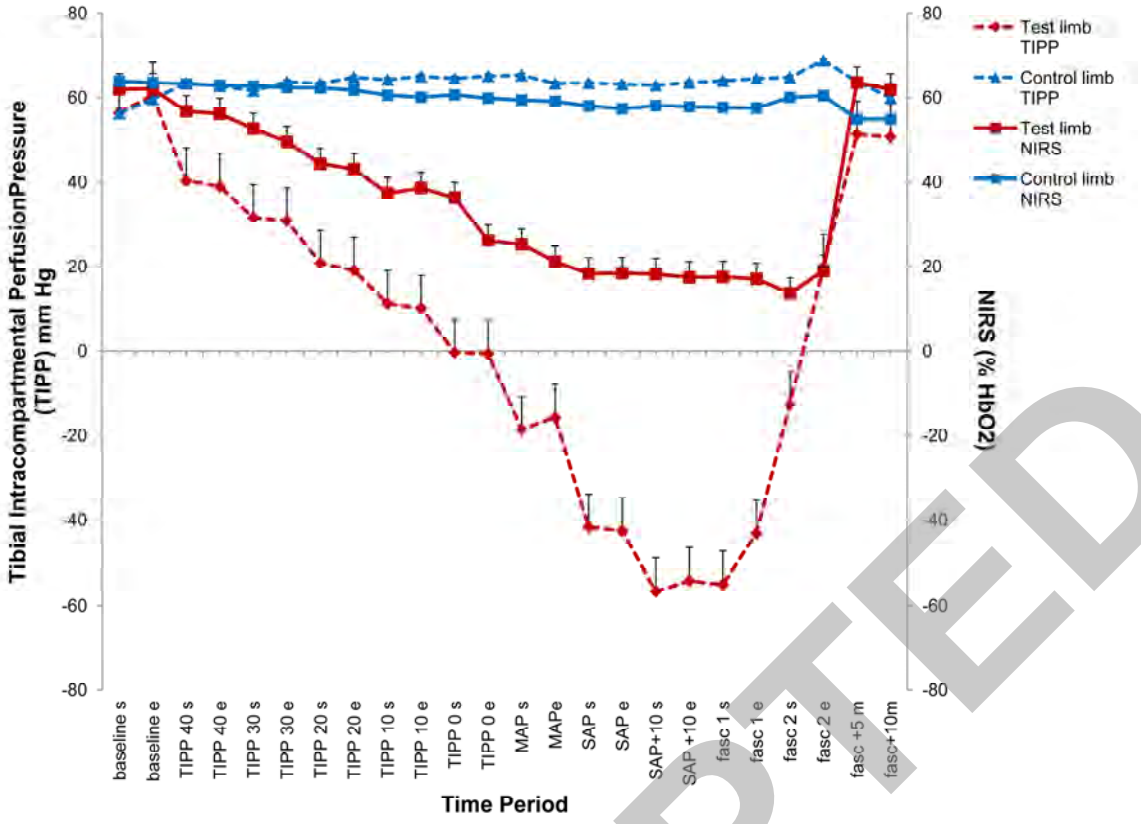
Table 1: NIRS and perfusion pressures from the two groups during the fasciotomy portion of the experiment.

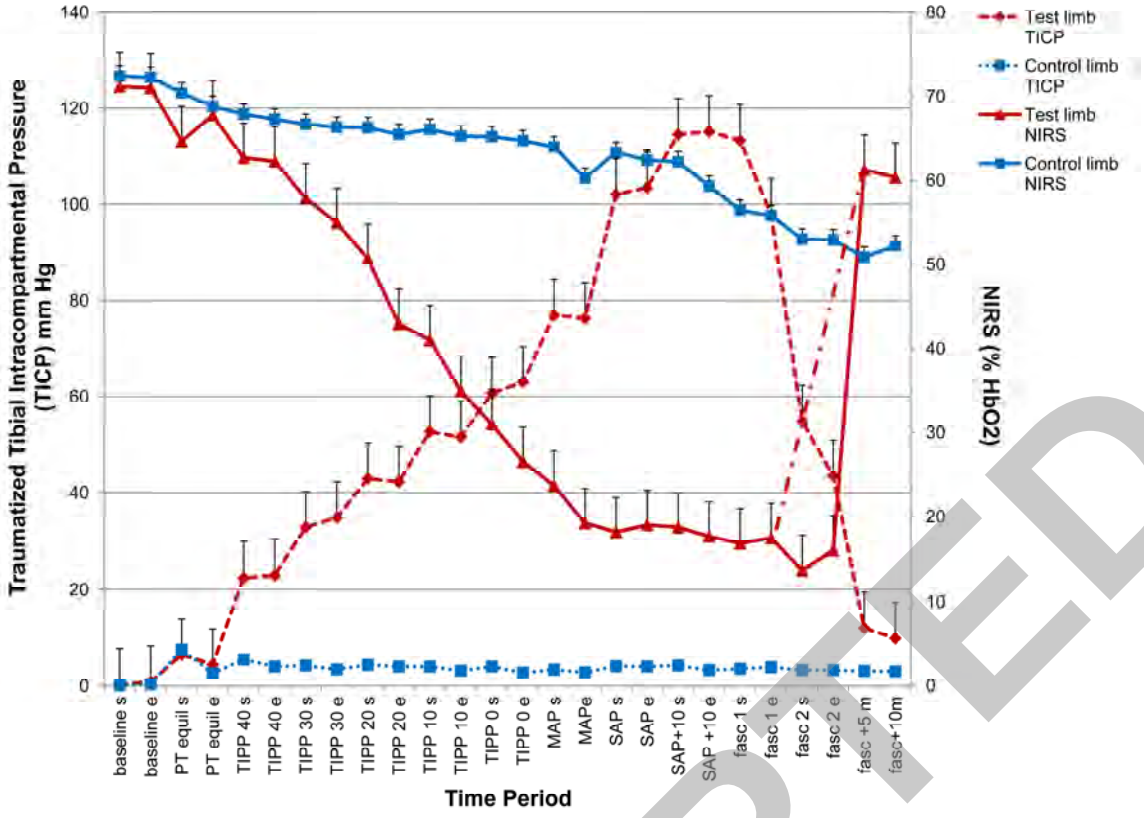
Control	Fasciotomy (1) n = 9		Fasciotomy (2) n = 7	
	NIRS Value	**Perfusion Pressure**	**NIRS Value**	**Perfusion Pressure**
Pre-first fasciotomy	23.8 ± 6.6	-49.0 ± 12.6	16.3 ± 0.5	-46.8 ± 26.7
30 seconds post 1st fasciotomy	24.5 ± 9.0	-16.4 ± 45.2	17.0 ± 0.0	-37.9 ± 32.2
60 seconds post 1st fasciotomy	40.2 ± 14.8	34.9 ± 18.8	16.0 ± 3.5	-26.6 ± 20.8
Post-2nd second fasciotomy				
30 seconds post 2nd fasciotomy	NA	NA	22.0 ± 11.7	33.5 ± 21.2
60 seconds post 2nd fasciotomy	NA	NA	35.3 ± 23.1	46.1 ± 13.3
Acute Trauma	**Fasciotomy (1) n = 4**		**Fasciotomy (2) n = 11**	
	NIRS Value	**Perfusion Pressure**	**NIRS Value**	**Perfusion Pressure**
Pre-first fasciotomy	24.7 ± 0.5	–52.1 ± 23.5	22.5 ± 4.1	-58.9 ± 22.8
30 seconds post 1st fasciotomy	35.0 ± 15.5	1.7 ± 22.6	23.5 ± 2.9	-36.4 ± 22.3
60 seconds post 1st fasciotomy	41.5 ±19.1	9.35 ± 35.4	21.7 ± 2.1	-5.86 ± 21.4
Post-2nd second fasciotomy				
30 seconds post 2nd fasciotomy	NA	NA	31.5 ± 12.7	33.6 ± 22.2
60 seconds post 2nd fasciotomy	NA	NA	43.1 ± 16.5	46.1 ± 13.3

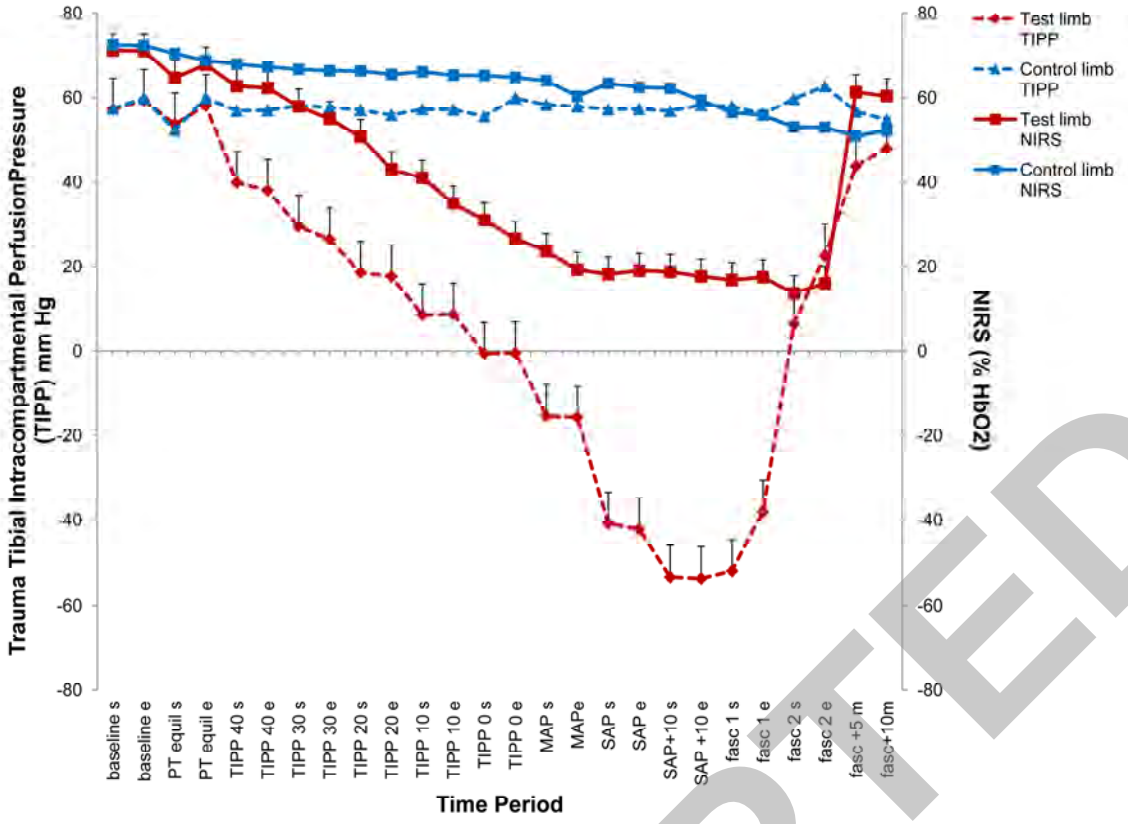
Table 1: NIRS and perfusion pressures from the two groups during the fasciotomy portion of the experiment.



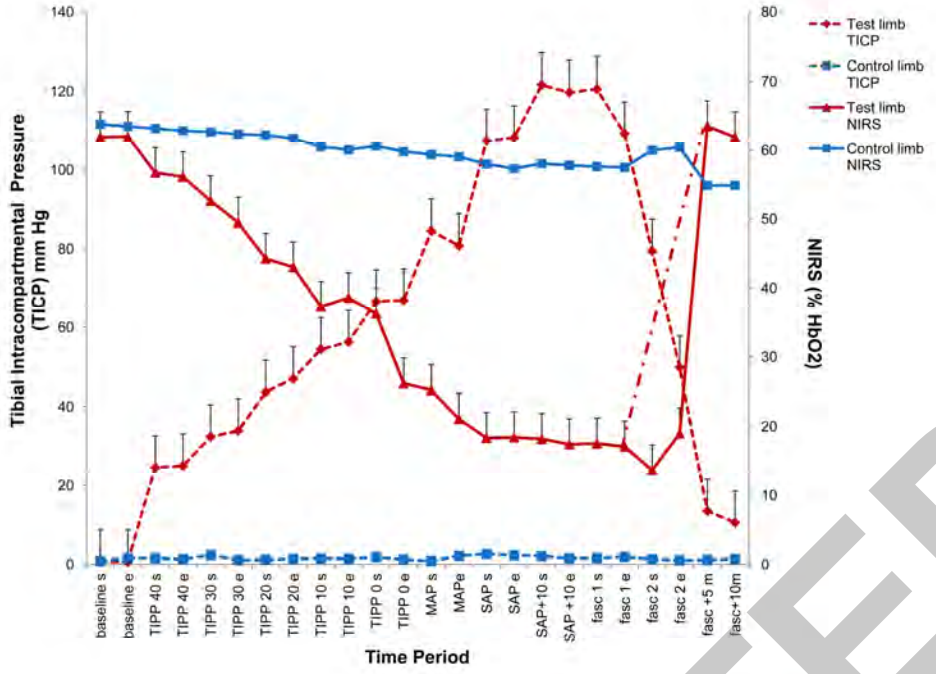




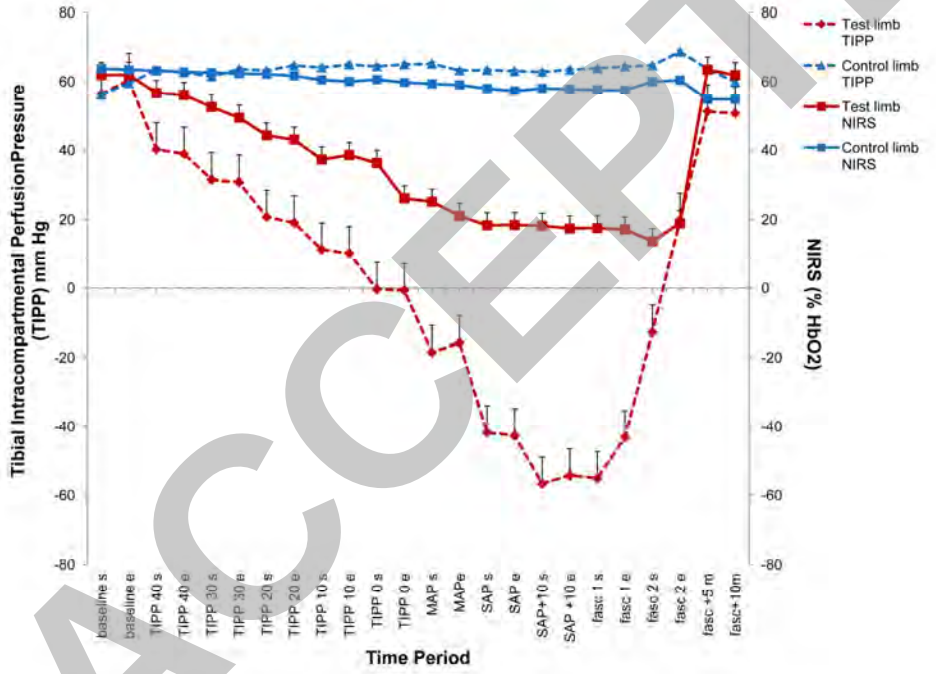




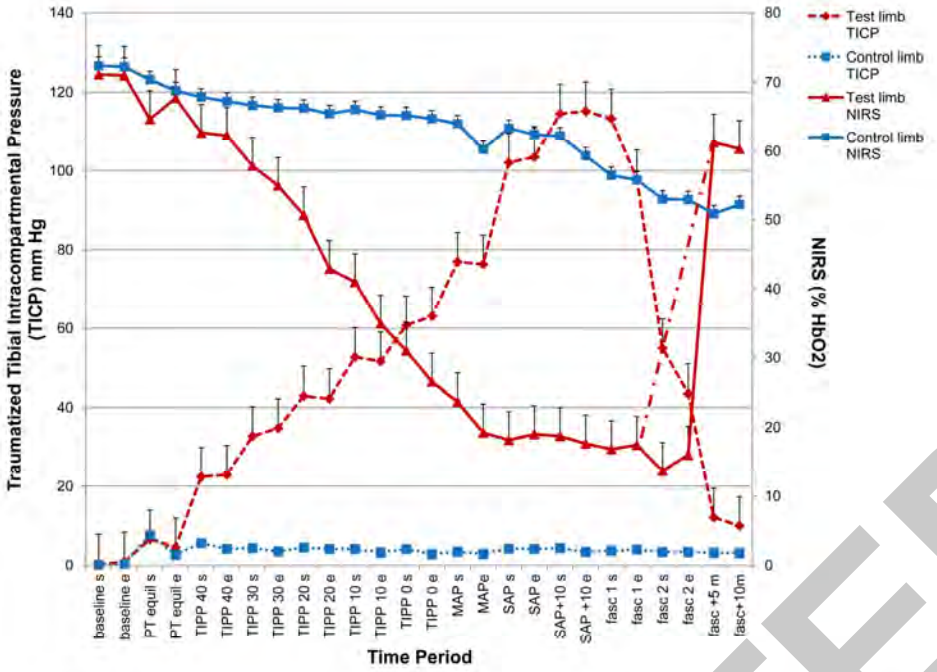
A.



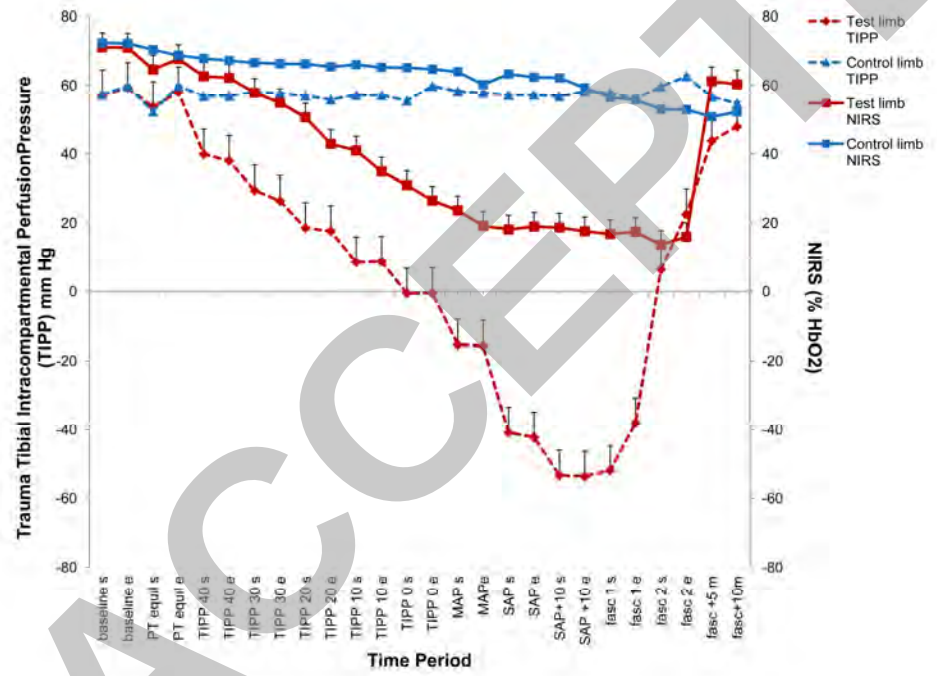
B.



A.



B.



Subcutaneous Depth in a Traumatized Lower Extremity

Roskosky, M., Robinson, G., Reisman, W., Ziran, B., Shuler, M., Freedman, B.

BACKGROUND

Acute compartment syndrome (ACS) is a condition that may develop in severely traumatized limbs when swelling and bleeding increases the pressure within non-expandable fascial compartments. When intra-compartmental pressure (ICP) approaches diastolic blood pressure, blood flow is cut off resulting in ischemia and necrosis [1]. Prevalence of ACS in patients with tibia fractures has been reported to be between 1% and 11% [2-5]. The universally accepted treatment for promptly diagnosed ACS is surgical release (4-compartment fasciotomy) allowing muscles to expand and re-perfuse.

Missed or delayed diagnosis of ACS can have devastating consequences including motor and sensory deficits, muscle contracture, increased risk of amputation, sepsis, rhabdomyolysis, multisystem organ failure and even death [6-9]. However, fasciotomies themselves are major surgical procedures that convert closed fractures to open fractures, delay fracture healing, and increase infection, morbidity, and disability [9]. Despite centuries of trying, accurate diagnosis of ACS has remained a challenge that relies heavily of physician experience and preference in evaluating subjective clinical signs and symptoms [5, 10, 11]. The only objective ACS diagnostic in common use is measurement of ICP. However, this is an invasive procedure that can produce erroneous results if not performed correctly [12-14] and validated diagnostic thresholds have been questioned [15-17]. Furthermore, ICP measurements are single points in

time, whereas ACS is a condition that evolves over time requiring serial monitoring over hours or days.

Use of near-infrared spectroscopy (NIRS) to directly measure tissue oxygenation may provide a noninvasive, continuous, and responsive solution for diagnosing ACS [18-20]. Light in the near-infrared (NIR) range (600 to 1000 nm) can penetrate skin, soft tissue and bone and is absorbed by hemoglobin in the muscle capillary beds. Using three different wavelengths of NIR light that are absorbed differentially by oxygenated and deoxygenated hemoglobin, the percent oxygen saturation (rSO_2) of hemoglobin in the muscle tissue can be calculated by measuring the amount of each wavelength that is reflected back to the sensor [21, 22]. Animal and clinical studies have confirmed the ability of NIRS technology to monitor perfusion in muscle compartments of the lower leg in the normal, hypoxic, and traumatized settings [23,24]. In human studies rSO_2 evaluated using NIRS decreased significantly in extremities diagnosed with ACS as compared to the uninjured contralateral extremity, and increased in response to fasciotomy [23, 24].

Since NIRS samples tissue at a depth of 2 to 3 cm, depending on the spacing between the light transmitter and receptor on the sensor pad [21, 22], concern has been raised regarding the ability to accurately measure intramuscular rSO_2 in leg compartments that are swollen or in obese patients. The purpose of this study was to measure the thickness of the subcutaneous tissue overlying the posterior muscle compartment in subjects with tibia fractures to determine if it might compromise rSO2 measurement in the muscle. Internal analysis of our previous clinical work indicated that the subcutaneous tissue layer is thickest over the superficial posterior compartment. Further this compartment is dependent in the supine position.

METHODS

This study is part of a larger study designed to validate the utility of continuous NIRS monitoring to diagnose ACS. The study was conducted at Grady Memorial Hospital, Atlanta Medical Center, and Athens Regional Medical Center in the State of Georgia from March 2012 to September 2013. The study was approved by each site's Institutional Review Board. It was funded by a grant from the Department of Defense, and approved by the Army's Human Research Protections Office.

The Nonin Medical Inc. Equanox^{TM} model 7600 oximeter and regional sensors (model 8003CA) were used for this study. These oximeters have four NIRS recording channels and three oximeters were used per subject to cover the twelve muscle compartments being monitored. The three units were connected via USB cable to a laptop that operated the proprietary data collection software and combined the NIRS data into a single spreadsheet.

Subjects were aged 18 to 65 and were recruited from the patients presenting to the respective trauma units with high energy tibia fractures or gunshot wounds to the leg with or without fracture. After obtaining informed consent from the patient (or a legally authorized representative), NIRS sensors were placed on the skin overlying the four compartments on the injured leg, the four compartments on the contralateral leg, and on four control compartments (both feet and the deltoid and volar compartments of one upper extremity). Ideally sensors were placed in line along the junction of the proximal and middle third of each leg compartment, but could be moved proximally or distally along the axis of the compartment to avoid placement

over wounds or hematomas, or to improve the quality of the NIRS signal. The intention in the protocol was to record continuous NIRS data for up to 48 hours with a possible extension to 72 hours if the treating physician considered that a risk for ACS existed. Subjects were considered to have a usable data set and had completed study participation if they had at least two hours of continuous NIRS data recorded.

Depth of tissue between the skin and the muscle fascia, or adipose tissue thickness (ATT) was measured over the superficial posterior compartment of both legs using a portable ultrasound device (BodyMetrix BX2000) connected via USB to a laptop that operated the BodyMetrix software. This device emits an ultrasonic wave that echoes back at different amplitudes as it reaches the interface between each unique tissue layer (i.e. subcutaneous, muscle, bone). The depths of these interfaces are recorded in millimeters, accurate to +/- 0.2mm. A recent review in the Journal of Obesity found ultrasounds to be a "reliable, reproducible and accurate way to measure subcutaneous fat."[25] In order to control for differences in operator proficiency, all research coordinators tasked with performing these measurements were extensively trained and followed a strict protocol. The superficial posterior compartment (back of calf) was used since it has the thickest subcutaneous layer. The subcutaneous layer is composed mainly of adipose and interstitial tissue, and may be increased in depth after trauma by accumulation of interstitial fluid. Depth measurements were taken over the site of optimal sensor placement (roughly two finger breadths posteromedially to the flexor digitorum longus along the junction of the proximal and middle third of the leg) at the time of enrollment.

Demographic data was recorded for each subject from the medical records including age, gender, race and ethnicity, height and weight, and body mass index (BMI) was calculated as weight (kg) / height $(m)^2$.

A total of 95 subjects completed participation in this study – 68 at GMH, 15 at AMC, and 12 at AMRC. This analysis was restricted to the 68 GMH subjects to reduce inter-site variability. Of these subjects 53 had ATT measured by ultrasound on both the injured and uninjured legs. Subjects for whom subcutaneous depth measurements were not taken, either had a splint placed over the injured leg for the subject's entire participation in the study or injuries over the superficial posterior compartment of either leg that prevented the measurement from being taken. Three subjects with bilateral tibial fractures were also removed from the analysis. The final dataset consisted of 50 subjects.

Statistics were performed using STATA12 (College Station, TX) for equality of means testing and Pearson's correlation. Statistical significance was accepted at p values < 0.05.

The institutional review boards at Emory University (Atlanta, GA), Atlanta Medical Center (Atlanta, GA), and Western IRB (Olympia, WA) provided approval to conduct this research.

RESULTS

Subject age ranged from 18 to 65 (mean: 39) years with 43 male and 7 female patients. The majority of patients were African-American (68%) and Caucasian (28%). The right leg was injured in 62% of cases. No significant trends in ATT were found based on gender, age, or race.

The mean subcutaneous ATT was 6.98 mm (sd: 3.17; range: 2, 14.3) for the injured leg, and 7.06 mm (sd: 3.37; range: 2.4, 16.1) for the uninjured contralateral leg. A breakdown of ATT by injury type can be seen in Table 1. Injured and uninjured ATT displayed a strong, positive correlation ($r=0.72$) that was statistically significant ($\alpha=0.05$) [Figure 1]. Mean body mass index (BMI) for the group was 27.08, with 20% of subjects falling in the obese category of 30kg/m^2 or higher. No significant correlation was found between the ATT of the injured or uninjured legs and BMI ($r=0.2$; Figures 2 – 3). Mean comparison testing revealed no difference in ATT between the injured and uninjured legs (null hypothesis: equal means; $p>>0.05$). Out of the 50 subjects analyzed, no subject had a subcutaneous depth of over 2 cm on the injured or uninjured leg. When the ATT of the uninjured leg was subtracted from that of the injured leg the result was slightly negative -0.84 mm (sd: 2.439; range: -6.7, 8.3). Means comparison testing revealed no change in the difference observed based on gender or race.

DISCUSSION

ACS is a condition that, if not appropriately diagnosed and treated, can have devastating outcomes with increased morbidity and mortality [6-9]. Current diagnosis is challenging and equivocal, relying on physician experience in evaluating subjective clinical signs and symptoms [5, 10, 11]. We have been investigating the direct measurement of tissue oxygen levels using NIRS as a tool for diagnosing ACS. Since NIRS has a tissue penetration of 2 to 3 cm below the skin [21, 22], concern has been raised as to whether it can reliably penetrate into the muscle tissue, particularly in subjects with significant subcutaneous adipose tissue or swelling. This study was designed to measure the distance between the skin and muscle fascia to confirm that

NIRS can adequately penetrate the subcutaneous space in obese patients or those with traumatically-induced subcutaneous swelling.

The study population included 50 patients with high energy tibia fractures who were at risk of developing ACS, and from whom ATT measurements could be obtained over the superficial posterior compartments of both lower extremities. There was no significant difference in the depth of subcutaneous tissue between the injured and uninjured contralateral legs of these 50 subjects indicating that traumatically-induced swelling is not affecting the distance from the skin to the muscle compartment. The significant swelling that occurs after injury is confined to the muscle compartment which, in fact, may actually compress the subcutaneous layer as only a slight decrease in tissue thickness of the uninjured leg was observed.

All subjects had a subcutaneous tissue depth of less than 2 cm, even in the 10 subjects that were clinically obese (BMI > 30). Obesity should not be a limiting factor to using NIRS to measure muscle tissue oxygenation. Further, BMI was a poor indicator for subcutaneous tissue depth with only a weak and non-significant correlation. Body fat deposition is typically not distributed around the lower leg in obese patients.

This study does not prove that NIRS can accurately measure muscle rSO_2 in injured lower extremities, but it quells concern over subcutaneous tissue thickness being an impediment to monitoring the underlying muscle even in obese patients, or those with significant traumatically-induced swelling. Although we did not measure the subcutaneous depth over the other lower leg compartments, the ATT is greatest over the superficial posterior compartment. One limitation to

this study is that subcutaneous depth could not always be measured in the exact same location on both legs since it was often difficult to move the injured leg into a suitable position for measurement.

This study demonstrates that the distance between the skin and the muscle tissue is less than the NIRS penetration distance (2-3cm) even in patients with significant subcutaneous adipose tissue or swelling, and should not limit its use as a tool to monitor muscle tissue oxygenation.

AUTHOR CONTRIBUTIONS

M.R. and G.R. conducted the literature search and managed data collection. B.F., M.S., W.R., and B.Z. were responsible for the design of the study. M.R. conducted the statistical analysis. M.R., G.R., M.S., and B.F. contributed equally to data interpretation, writing, and critical revision.

REFERENCES

1. Heckman MM, Whitesides TE, Grewe SR, Judd RL, Miller M, Lawrence JH (1993) Histological Determination of the Ischemic Threshold of Muscle in the Canine Compartment Syndrome Model. *Journal of Orthopaedic Trauma* 7(3): 199 – 210.

2. Branco BC, Inaba K, Barmparas G, Schnuriger B, Lustenberger T, Talving P, Lam L, Demetriades D (2010) Incidence and predictors for the need for fasciotomy after extremity trauma: A 10-year review in a mature level I trauma center. *Injury* 42(10) 1157 – 1163.

3. Keating JF, O'Brien PI, Blachut PA, Meek RN, Broekhuyse HM (1997) Reamed interlocking intramedullary nailing of open fractures of the tibia. *Clinical Orthopaedics and Related Research* 338: 182 – 191.

4. Court-Brown CM, Will E, Christie J, McQueen MM (1996) Reamed or undreamed nailing for closed tibial fractures: A prospective study in Tscherne C1 fractures. *Journal of Bone and Joint Surgery [British]* 78: 580 – 583.

5. O'Toole RV, Whitney A, Merchant N, Hui E, Higgins J, Kim TT, Sagebien C (2009) Variation in diagnosis of compartment syndrome by surgeons treating tibial shaft fractures. *J Trauma* 67: 735 – 741.

6. Finkelstein JA, Hunter GA, Hu RW (1996) Lower limb compartment syndrome: Course after delayed fasciotomy. *J Trauma* 40: 3432 – 344.

7. McQueen MM, Christie J, Court-Brown CM (1996) Acute compartment syndrome in tibial diaphyseal fractures. *Journal of Bone and Joint Surgery [British]* 78-B: 95 – 98.

8. Williams AB, Luchette FA, Papaconstantinou HT, Lim E, Hurst JM, Johannigman JA, Davis KD (1997) The effect of early versus late fasciotomy in the management of extremity trauma. *Surgery* 122: 861 – 866.

9. Ritenour AE, Dorlac WC, Fang R, Woods T, Jenkins DH, Flaherty SF, Wade CE, Holcomb JB (2008) Complications after fasciotomy revision and delayed compartment release in combat patients. *The Journal of Trauma, Injury, Infection, and Critical Care* 64: S153 – S162.

10. Olson SA, Glasgow RR (2005) Acute compartment syndrome in lower extremity musculoskeletal trauma. *Journal of the American Academy of Orthopaedic Surgeons* 13: 436 – 444.

11. Ulmer T (2002) The clinical diagnosis of compartment syndrome of the lower leg: Are clinical findings predictive of the disorder? *Journal of Orthopaedic Surgery and Sports Medicine* 16(8) 572 – 577.

12. Heckman MM, Whitesides TE, Grewe SR, Rooks MD (1994) Compartment pressure in association with closed tibial fractures: The relationship between tissue pressure, compartment, and the distance from the site of the fracture. *Journal of Bone and Joint Surgery [Am]* 76: 1285 – 1292.

13. Uliasz A, Ishida JT, Fleming JK, Yamamoto LG (2003) Comparing the methods of measuring compartment pressures in acute compartment syndrome. *American Journal of Emergency Medicine* 21: 143 – 145.

14. Boody AR, Wongworawat MD (2005) Accuracy in the measurement of compartment pressures: A comparison of three commonly used devices. *Journal of Bone and Joint Surgery [Am]* 87: 2415 – 2422.

15. McQueen MM, Court-Brown CM (1996) Compartment monitoring in tibial fractures: The pressure threshold for decompression. *Journal of Bone and Joint Surgery [Br]* 78: 99 – 104.

16. Ozkayin N, Aktuglu K (2005) Absolute compartment pressure versus differential pressure for the diagnosis of compartment syndrome in tibial fractures. *International Orthopaedics (SICOT)* 29: 396 – 401.

17. Kosir R, Moore F, Selby JH, Cocanour CS, Kozar RA, Gonzalez EA, Todd SR (2007) Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *J Trauma* 63: 268 – 275.

18. Arbabi S, Brundage SI, Gentilello LM (1999) Near-infrared spectroscopy: A potential method for continuous, transcutaneous monitoring for compartmental syndrome in critically injured patients. *J Trauma* 47: 829-833.

19. Garr JL, Gentilello LM, Cole PA, Mock CN, Matsen FA (1999) Monitoring for compartmental syndrome using near-infrared spectroscopy: A noninvasive, continuous, transcutaneous monitoring technique. *J Trauma* 46: 613 – 618.

20. Giannotti G, Cohn SM, Brown M, Varela JE, McKenney MG, Wiseberg JA (2000) Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. *J Trauma* 48: 396 – 401.

21. Arimoto H, Egawa M, Yamada Y (2005) Depth profile of diffuse reflectance near-infrared spectroscopy for measurement of water content in skin. *Skin Research Technology* 11: 27 – 35.

22. Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC (2000) Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. *Journal of Clinical Monitoring and Computing* 16: 191 – 199.

23. Shuler MS, Reisman WM, Whitesides TE, Kinsey TL, Hammerberg EM, Davila MG, Moore TJ (2009) Near-infrared spectroscopy in lower extremity trauma. *Journal of Bone and Joint Surgery [Am]* 91: 1360 – 1368.

24. Shuler MS, Reisman WM, Kinsey TL, Whitesides TE, Hammerberg EM, Davila MG, Moore TJ (2010) Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *Journal of Bone and Joint Surgery [Am]* 92: 863 – 870.

25. Wagner, D (2013) Ultrasound as a tool to assess body fat. Journal of Obesity, 9 pages. doi: 10.1155/2013/280713.

FIGURES

Figure 1: Correlation of ATT of injured versus uninjured legs revealed a strong positive correlation that was statistically significant (r = 0.7230; p=0.000; α=0.05).

Figure 2: Correlation of ATT of the injured leg vs BMI revealed a weak positive correlation that was non-significant (r = 0.2041; p=0.1551; α=0.05).

Figure 3: Correlation of ATT of the uninjured leg vs BMI revealed a weak positive correlation that was non-significant (r = 0.2033; p=0.1568; α=0.05).

Subcutaneous depth in a traumatized lower extremity

Mellisa Roskosky, MSPH
Athens Orthopedic Clinic
1765 Old West Broad St.
Building 2, Suite 200
Athens, GA 30605
Mellisa.nirs@gmail.com
(706) 433 – 4031
Gillian Robinson, PhD
25074 NW 210th Lane
High Springs, FL 32643
grobinson@genevausa.org
(386) 454 – 7890
Brett Freedman, MD
Landstuhl Regional Medical Center
Landstuhl, Germany
brett.freedman@amedd.army.mil
Michael Shuler, MD
Athens Orthopedic Clinic
1765 Old West Broad St.
Building 2, Suite 200
Athens, GA 30605
msimmss@hotmail.com
(706) 433 – 4022

INTRODUCTION

Acute compartment syndrome (ACS) is a rare but serious consequence of traumatic leg injury. This ongoing observational cohort study aims to validate the use of Near Infrared Spectroscopy (NIRS) for continuous monitoring of oxygen saturation in the muscles of the leg and diagnosis of ACS as an alternative to invasive pressure monitoring. NIRS is able to measure oxygenation to a depth of 2 to 3 cm below the skin, raising concerns over the ability of NIRS to accurately determine oxygenation of injured leg compartments in the presence of swelling and in the obese. The hypothesis was that NIRS is able to accurately measure oxygenation in injured legs despite these circumstances.

METHODS

Data was analyzed on 79 patients with severe leg injuries, including qualifying tibia fractures and gunshot wounds, who presented to a participating trauma center within 12 hours of injury. Distance from skin to fascia in the superficial posterior compartment of both legs was measured on each patient using a portable ultrasound device. The superficial posterior compartment was chosen since the thickest layer of subcutaneous fat is in this area.

RESULTS

Subject age ranged from 18 to 65 (mean: 39.04) years with 64 male and 15 female patients. The mean subcutaneous adipose tissue thickness (ATT) was 7.65 mm (range: 2, 22.6) for the injured leg, 7.62 mm (range: 2.4, 18.9) for the uninjured contralateral leg and mean body mass index (BMI) for the group was 26.56. No significant correlation was found between the ATT of the injured or uninjured legs and BMI. Mean comparison testing revealed no difference in adipose tissue thickness between the injured and uninjured legs (null hypothesis: equal means; statistically significant). Out of the 79 enrolled subjects, only one subject had a subcutaneous depth of over 2 cm on the injured leg.

DISCUSSION AND CONCLUSION

These data suggest that, within this traumatically injured population, symptoms associated with leg injury (such as swelling and edema) do not significantly affect the distance from skin to fascia. It is also notable that subcutaneous depth beyond the 2cm mark (validated in previous studies) is a rare occurrence in this population. These results further support the use of continuous NIRS monitoring for diagnosis of ACS.

Evaluation of NIRS, serum biomarkers and muscle damage in a porcine balloon compression model of acute compartment syndrome

Steven Budsberg, Michael Shuler, Brett Freedman, Megan Hansen.

Purpose: Correlate near infrared spectroscopy (NIRS), tibial intra-compartmental pressure (TICP), tibial intra-compartmental perfusion pressure (TIPP), serum markers of inflammation and muscle injury in a balloon compression model of acute compartment syndrome (ACS).
Methods: Six landrace swine had NIRS sensors placed on each leg. Balloon catheters were inflated below the cranial tibialis (CT) muscle and deflated at 6 hours. Systolic, diastolic, and mean arterial pressures, compartmental pressures, and oximetry were measured prior to and during balloon inflation. Measurements continued 5, 10 15, 30, 45, 60 minutes and hourly for 8 hours. At euthanasia, CT muscle was collected for muscle damage scoring. Serum creatine kinase (CK), myoglobin, TNF-α, IL-1β, IL-6 were measured.
Results: Test limb TIPP significantly decreased at balloon inflation and at 15 minutes post deflation through 8 hours. TICP significantly increased during balloon inflation and from 1 to 6 hours after deflation. NIRS measurements were significantly lower following balloon inflation. Myoglobin concentrations significantly increased following balloon deflation. CK concentrations significantly increased from 2 hours post deflation, CT muscle degeneration, and necrosis scores were significantly higher. There was a significant correlation of muscle degeneration and edema with NIRS.
Conclusions: This model provided evidence that NIRS may indirectly assess muscle changes in ACS development.

Topic Area: Extremity Trauma, Monitors and Sensors

Learning Points: This research sheds further light on Near Infrared Spectroscopy (NIRS) in assessing Acute Compartment Syndrome (ACS) in traumatized lower extremities

Subcutaneous Depth in a Traumatized Lower Extremity

Mellisa Roskosky, Gillian Robinson, Michael Shuler, Brett Freedman

Purpose: Acute compartment syndrome (ACS) is a rare but serious consequence of traumatic leg injury. This study aims to validate the use of Near Infrared Spectroscopy (NIRS) for continuous monitoring of oxygen saturation in the muscles of the leg and diagnosis of ACS as an alternative to invasive pressure monitoring. NIRS is able to measure oxygenation to a depth of 2-3cm below the skin, raising concerns over the ability of NIRS to accurately determine oxygenation of injured leg compartments in the presence of swelling and in the obese.
Methods: Data was analyzed on 51 patients with severe leg injuries. Distance from skin to fascia in the superficial posterior compartment of both legs was measured on each patient using a portable ultrasound device.
Results: Subject age ranged from 20-64years with 43 male and 8 female patients. The mean subcutaneous adipose tissue thickness was 7.75 and 7.68mm for the injured and uninjured legs respectively. Mean comparison testing revealed no difference in adipose tissue thickness between the injured and uninjured legs. Only one subject had a subcutaneous depth of over 2cm on the injured leg.
Conclusion: These data suggest that, within this population, symptoms associated with leg injury do not significantly affect the distance from skin to fascia. It is also notable that subcutaneous depth beyond the 2cm mark is a rare occurrence in this population. These results further support the use of continuous NIRS monitoring for diagnosis of ACS.

Character Count (including spaces): 1500 (Max 1500)

Topic Area: Injury Dosimetry, Monitors and Sensors

Learning Points: This research sheds further light on the utility of Near Infrared Spectroscopy (NIRS) for monitoring muscle oxygenation and diagnosis of Acute Compartment Syndrome (ACS) in traumatized lower extremities.

Subcutaneous Depth in a Traumatized Lower Extremity

Mellisa Roskosky, Mark Guevorkian, Gillian Robinson, Brett Freedman, Michael Shuler

INTRODUCTION

Acute compartment syndrome (ACS) is a rare but serious consequence of traumatic leg injury. This ongoing observational cohort study aims to validate the use of Near Infrared Spectroscopy (NIRS) for continuous monitoring of oxygen saturation in the muscles of the leg and diagnosis of ACS as an alternative to invasive pressure monitoring. NIRS is able to measure oxygenation to a depth of 2 to 3 cm below the skin, raising concerns over the ability of NIRS to accurately determine oxygenation of injured leg compartments in the presence of swelling and in the obese.

METHODS

Data was analyzed on 51 patients with severe leg injuries, including qualifying tibia fractures and gunshot wounds, who presented to a participating trauma center within 12 hours of injury. Distance from skin to fascia in the superficial posterior compartment of both legs was measured on each patient using a portable ultrasound device.

RESULTS

Subject age ranged from 20 to 64 (mean: 39.2) years with 43 male and 8 female patients. The mean subcutaneous adipose tissue thickness was 7.75mm for the injured leg and 7.68mm for the uninjured contralateral leg. Mean comparison testing revealed no difference in adipose tissue thickness between the injured and uninjured legs. Out of the 51 enrolled subjects, only one subject had a subcutaneous depth of over 2cm on the injured leg.

DISCUSSION AND CONCLUSION

These data suggest that, within this traumatically injured population, symptoms associated with leg injury (such as swelling and edema) do not significantly affect the distance from skin to fascia. It is also notable that subcutaneous depth beyond the 2cm mark (validated in previous studies) is a rare occurrence in this population. These results further support the use of continuous NIRS monitoring for diagnosis of ACS.

Word Count: 300 (Max 300)